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An Advance Market Commitment for AIDS Vaccines: Accelerating the Response from Industry

IAVI Public Policy Department

This paper was written by Paul Wilson (Columbia University), John Hurvitz (Covington & Burling), Barbara O'Hanlon (O'Hanlon Health Consulting), and Sarah Post (IAVI). The work was directed by Robert Hecht (IAVI).

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An Advance Market Commitment for AIDS Vaccines: Accelerating the Response from Industry

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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.

Preface

This report was conceived and written during 2005, when our goal was to apply the overall Advance Market Commitment (AMC) concept to AIDS vaccines and to contribute to the larger process of creating a significant global AMC program, following the G8 heads of state endorsement in July 2005 of AMCs as a promising way to accelerate development of new vaccines.

Since the time the consultation draft of this report was completed in October 2005, significant positive advances have occurred in the thinking and actions on AMCs. The Italian Ministry of Finance prepared a report on AMCs in October-November 2005, which was presented to the G7 Finance Ministers in December. At that time, they announced their intention to implement a pilot AMC program and enlisted the GAVI Alliance and the World Bank to coordinate this initiative.

During the first three months of 2006, the GAVI-World Bank AMC team met with an Advisory Group composed of vaccine experts (including IAVI), reached out to industry and biotech representatives, and convened an independent Expert Committee to evaluate and prioritize six new vaccines (including AIDS as well as malaria, tuberculosis, human papilloma virus, rotavirus, and pneumococcus) for the AMC pilot. On this basis, GAVI and the World Bank made recommendations to the G7 Finance Ministers, who reviewed these at an April 2006 meeting in Washington and "call[ed] for the additional work necessary to make [the pilot AMC's] launch possible in 2006." So it appears likely that an AMC will become a reality some time this year for some new vaccine(s). In this regard, IAVI's AMC work may already have made a positive contribution.

In the meantime, our AMC activities have also continued to evolve in recent months. We are examining the size of the potential market for an AIDS vaccine in the rich countries of North America, Europe, and Japan, in order to factor these markets correctly into our assessment of an AMC's incentive effects. While we continue to explore the possible impact of AMCs (and other incentives) on industry decisions to invest in upstream research and development, we are also modeling the effects of an AMC on the more advanced AIDS vaccine candidates in the current pipeline, such as the adenovirus-based vaccines developed by Merck and by the NIH's Vaccine Research Center. For these candidates, an AMC's objective would be to encourage companies to scale up manufacturing capacity (rather than expanding vaccine research and early product design and testing), in order to accelerate the vaccine's availability in low-income countries of Africa, Asia, and Latin America. If the current vaccine trials yield promising results, an AMC could be an important mechanism for ensuring that the developing world would have rapid access to the resulting products.

The extraordinary progress in recent months in international support for AMCs, along with our growing understanding of the multiple roles that AMCs and other incentives could play for the future of AIDS and other vaccines, are all part of an encouraging trend for those of us who are committed to fighting disease and poverty around the world.

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Acronyms

AIDS	Acquired Immune Deficiency Syndrome
AMC	Advance Market Commitment
ART	Antiretroviral therapy
BVGH	BIO Ventures for Global Health
CGD	Center for Global Development
DALY	Disability-adjusted life year
EMEA	European Medicines Agency
EPI	Expanded Program on Immunization
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
HPV	Human papillomavirus
IAC	Independent Assessment Committee
IAVI	International AIDS Vaccine Initiative
ITBN	Insecticide-treated bed net
MVI	Malaria Vaccine Initiative
NCE	New chemical entity
NPV	Net present value
PMTCT	Prevention of mother-to-child transmission
R&D	Research and development
STI	Sexually transmitted infection
UNAIDS	Joint United Nations Program on HIV/AIDS
UNICEF	United Nations Children's Fund
VCT	Voluntary counseling and testing
WHO	World Health Organization

Executive Summary

The AIDS epidemic has continued its relentless expansion, killing three million people in 2005 even as five million more became infected with HIV. Antiretroviral treatment can extend lives and relieve suffering, but only prevention can halt and reverse the epidemic's spread. A preventive AIDS vaccine remains the best hope for a decisive victory over the epidemic, especially in the developing world.

Researchers face significant challenges in developing a broadly useful AIDS vaccine. These efforts will require increased investment in basic research, preclinical development, large-scale trials, and eventually manufacturing capacity. Moreover, bringing a vaccine to market will require much greater involvement by all segments of the private pharmaceutical industry, which brings unique expertise and resources to vaccine development. The private sector, which accounts for only 10 percent of current spending on AIDS vaccine R&D, has been deterred from greater investment not only by scientific uncertainty but also by market risks. The need for a vaccine is greatest in the countries that are least able to pay; in addition, firms fear that political pressures would compel them to provide a vaccine at a very low price.

An advance market commitment (AMC) for AIDS vaccines – a legally binding commitment by donors to pay an agreed price for a qualifying vaccine – could motivate greater private sector investment in vaccine development by increasing expected returns from sales in the poorest countries and by alleviating political risks. Moreover, an AMC could speed adoption of a vaccine in developing countries by guaranteeing secure supply at an affordable price. An AMC would not substitute for continued direct support for vaccine R&D or for vitally needed improvements in vaccine procurement and delivery. But an AMC could work together with push funding and improvements in vaccine systems to accelerate development, manufacture, and adoption of an AIDS vaccine.

The recent report by the Center for Global Development, *Making Markets for Vaccines: Ideas to Action*, described the potential benefits of AMCs for vaccines and outlined the general structure of a feasible and credible commitment. The IAVI team applied this general framework to the case of AIDS, proposing specific terms for an AIDS vaccine AMC, testing these proposals in meetings with officials from the pharmaceutical and biotechnology industries, and estimating the social benefits of an AMC.

The terms of an AMC for AIDS vaccines

An advance market commitment would be embodied in two contracts, a Framework Agreement establishing the terms of the offer and creating a binding obligation on sponsors, and a Guarantee Agreement allowing firms with a qualifying vaccine to receive the guaranteed price in return for an obligation to supply vaccine to eligible low-income countries. The specific terms of the agreement would include:

- vaccine eligibility requirements;
- the guarantee price and country co-payment;
- the maximum quantity to which the guaranteed price would apply;

- a reduced price that would apply after the guarantee commitment had been exhausted (or a mechanism for determining this price); and,
- a definition of eligible countries.

Setting technical specifications for a product that may not be developed for many years poses obvious challenges. For an AIDS vaccine, these standards must be based as much on the likely benefits of products with different characteristics as on the features of candidates currently in the development pipeline. Based on an analysis of vaccine impact and cost-effectiveness and other considerations, the IAVI team concluded that an AIDS vaccine should have at least 50 percent efficacy and five-year duration to qualify for purchase under an AMC. Both vaccines that prevent infection and those that reduce disease progression could qualify. Since information on duration of protection might be incomplete at the time of licensure, otherwise qualifying vaccines would be eligible for purchase at a reduced price until the standard had been met; payments would then be topped up retrospectively. Vaccines would have to be approved by one of a set of qualified regulatory agencies or be prequalified by the World Health Organization (WHO). They would have to confer protection in no more than three doses and meet additional standards covering presentation and ease of use in resource-poor settings.

To preserve flexibility and ensure that a potentially useful vaccine is not rejected unnecessarily, the Independent Assessment Committee (IAC), the body responsible for determining whether the eligibility requirements had been met, would have the power to waive any of the standards in certain circumstances. Although the details of these proposed standards can certainly be debated, we conclude that AMC sponsors could feasibly set technical specifications for a vaccine well in advance of a viable product.

On the basis of revenues for existing pharmaceutical products, the CGD report concluded that an AMC should bring the total market for a vaccine to at least $3 billion to stimulate private sector investment. The prospective market for an AIDS vaccine would almost certainly have to be larger to compensate for the unusually high scientific risks; we propose aiming for a total market of at least $4 billion. Taking into consideration the expected market in developed and middle-income countries, this would imply an AMC with net present value of $3.3 billion at the time of first sales. This approach to determining the size of an AMC is particularly well suited to AIDS vaccines, since it does not rely on detailed estimates of development risks and costs that are not available for very early-stage products.

The guaranteed price has emerged as the most contentious element of the proposed AMC. One crucial consideration in setting this price is how long the commitment can be expected to last before the agreed maximum quantity is reached. A higher price means a lower quantity (if the size of the AMC is fixed), which in turn implies an earlier end to the commitment, less opportunity for multiple vaccines to qualify, and greater risks for firms that fear they will not be first to market. But if an AMC is to attract new investment, the guaranteed price must also be well above likely manufacturing cost and compare favorably to what firms believe they may be able to charge in eligible markets in the absence of an AMC.

The IAVI team took as its starting point the premise that an AMC for AIDS vaccines should be designed to last about ten years, to support the development of both first

generation and improved vaccines and to ensure multiple suppliers. Based on relatively conservative demand projections, this requirement would be satisfied by a commitment to pay $24 per course of vaccination ($8 per dose for a three-dose vaccine) for up to 200 million courses. Under an alternative, higher-demand scenario, 300 million courses would be required over ten years, and the price would have to be lowered to $15 per course to keep the total commitment at $3.3 billion. Given these demand projections, sponsors could offer a higher price only by increasing the total value of the commitment or by shortening its duration. More optimistic assumptions about vaccine uptake would imply either an even larger or more rapidly exhausted commitment. Developing countries would pay a fraction of the guaranteed price, perhaps $6 (or $2 a dose). Since even this lower price could pose a substantial barrier to the poorest countries, development partners could choose to pay a portion of it.

More work needs to be done on mechanisms for setting the guaranteed price. The analysis presented here is intended primarily to illustrate the trade-offs between price and AMC size, projected demand, and expected duration, and to show how these considerations might be balanced. It should not be taken as an endorsement of a certain price as "fair" or "appropriate" for low-income countries or for other markets.

Firms that benefit from sales at the guaranteed price would be expected to continue providing vaccine to eligible countries at a price close to the cost of production. Since manufacturing costs will remain uncertain until a vaccine is developed, we propose choosing this long-term or "tail" price on the basis of affordability and long-run cost-effectiveness but making it subject to waiver by the IAC in certain circumstances. In this way, a firm might be able to receive a price higher than the one originally specified, if it turns out that its costs of goods is higher than originally anticipated and the vaccine confers larger health benefits than stipulated in the initial specifications for efficacy, duration of protection, etc. Firms would also be allowed to charge more than the agreed tail price if they had captured a relatively small share of sales at the guaranteed price. If, on the other hand, a firm finds that it can produce its vaccine for less than the agreed long-term price, we propose that it be allowed to lower this price and the country co-payment in order to attract additional sales.

Finally, we propose that all countries with per capita income below $1000, plus those with incomes of $1000-$5000 and HIV prevalence above five percent, be eligible to purchase vaccine under the AMC.

Industry response to the AMC proposal

The IAVI team presented its AMC proposal to officials of more than a dozen companies in the vaccine industry, including biotech firms, developing country manufacturers, and large pharmaceutical companies. Reaction to the AMC concept, and to the IAVI proposal, was generally positive, although many firms raised concerns with specific features of the proposal.

The most contentious elements of the proposed AMC were the guaranteed and long-term prices. Company officials were concerned that the proposed prices could prove too low to

provide an adequate return, given the possibility that AIDS vaccines will be more expensive to manufacture than existing vaccines. More generally, some were uncomfortable with setting prices in advance, before adequate information is available on costs. Other features of the proposed agreement, including the vaccine and country eligibility requirements and the provisions for second entrants, met with few objections.

There was no clear consensus on the central question whether an AMC of the proposed size could substantially increase industry investment in AIDS vaccines. Some firms felt that an AMC could increase the involvement of both large pharmaceutical and biotechnology companies, some were not convinced that the proposed incentive would be large enough to change industry behavior, and others were skeptical that even a large AMC would have much effect, citing scientific challenges. All firms, however, expressed support for the basic goals of an AMC and seemed interested in working with IAVI and potential sponsors to develop an AMC that could achieve these goals.

Impact and cost-effectiveness of an AMC

Potential sponsors have a natural interest in knowing what impact an AIDS vaccine AMC might have and whether it would prove a cost-effective investment. To answer this question, we analyzed the impact of an AMC under four scenarios, using a model adapted from the one that Michael Kremer and colleagues developed to explore the impact of vaccine AMCs in general. This analysis was based in turn on simple, relatively conservative projections of likely vaccine uptake. Our low-demand projection predicts that about 200 million people are vaccinated in eligible countries over the first 10 years, while more than 325 million are reached in the high-demand scenario.

Our analysis demonstrates that even a first generation vaccine with 50 percent efficacy and 10 year duration would save almost 100 million disability-adjusted life years (DALYs) and avert more than three million infections over the first ten years, even in the low-demand scenario. Its impact would be greater with higher uptake. The impact of a superior vaccine, with 80 percent efficacy and 20 year duration, would be substantially greater: in the high-demand scenario such a vaccine would avert more than 300 million lost DALYs and 10 million infections over ten years.

Purchasing either vaccine under the terms of the proposed AMC would be cost-effective. The total cost per DALY saved would range from $67 to as low as $21, which compares very favorably to other HIV/AIDS interventions and other health sector investments. Even if only the incremental benefits of bringing a vaccine into widespread use sooner are considered, an AMC is in most scenarios a very cost-effective use of donor funds.

These estimates of vaccine impact should be considered conservative, both because they rest on conservative projections of uptake and because they do not incorporate the potentially substantial indirect benefits of widespread vaccination.

Conclusions

The proposal presented here offers practical solutions to many of the issues surrounding an AMC for AIDS vaccines, including establishing technical specifications, prices, and other terms of an agreement well before much is known about the characteristics and cost of a vaccine. Consultations with industry suggest considerable if not unanimous enthusiasm for an AMC, although several difficult issues remain. Our modeling work confirms that an AIDS vaccine AMC would be a very cost-effective investment for sponsors and provides a preliminary, conservative estimate of the health impact of an AIDS vaccine in low-income countries.

The successful implementation of an AMC will require further work and consultation in several areas, particularly in establishing generally acceptable approaches to determining the size of an AMC and to setting the guaranteed and long-term prices. At its 2005 summit in Gleneagles, the G8 endorsed the concept of an AMC for critical diseases including AIDS, and has set into motion a process that can facilitate the additional work and consultations needed to implement an AMC for AIDS vaccine. We believe a well-designed, adequately funded AMC, together with strong direct support for R&D, could substantially accelerate progress toward an AIDS vaccine for the developing world.

1.0 Introduction

In the twenty years since the identification of HIV as the cause of AIDS, the HIV pandemic has become one of the greatest public health crises facing the world. According to UNAIDS, AIDS was responsible for 3.1 million deaths in 2005. There were 4.9 million new HIV infections, and about 40.3 million people are now infected with HIV.[1] At this pace, AIDS will take more lives than any other infectious disease in history. Although expanded prevention and treatment programs are helping address the illness and death associated with HIV and AIDS, the best hope to end the pandemic is a safe and effective preventive AIDS vaccine.

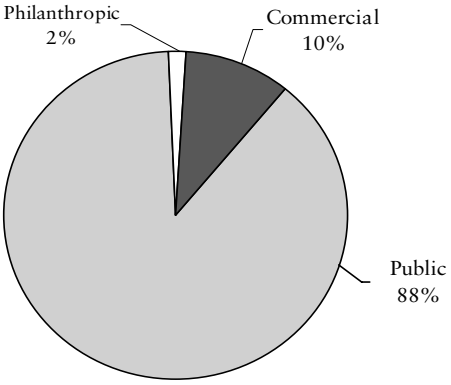
To develop an AIDS vaccine and to ensure its widespread use, governments, non-profit organizations, and industry around the globe will have to mobilize financial resources and scientific talent on a scale without precedent in the history of vaccines. This goal will be best achieved through a combination of "push" and "pull" measures and high-level political support.[2] Among pull incentives, advance market commitments (AMCs) – legally binding commitments by donors to pay an agreed price for a vaccine – have recently received much attention. An influential report from the Center for Global Development (CGD) argued that AMCs, as part of a larger set of policy actions including direct support for vaccines, could substantially accelerate development and adoption of vaccines for diseases of the developing world.[3] This report explores the feasibility and value of an AMC for AIDS vaccines.

1.1 Rationale for an AIDS vaccine AMC – engaging industry in R&D

Expenditures on AIDS vaccine research and development (R&D) have grown significantly, from approximately US$ 160 million in 1993[4] to an estimated US$ 690 million in 2004.[5] Despite this growth, total annual spending on AIDS vaccine research and development (R&D) represents less than one percent of expenditures on all health R&D.[6]

[1] UNAIDS. AIDS Epidemic Update. Geneva: UNAIDS, 2005.
[2] IAVI. Incentives for private sector development of an AIDS vaccine. Policy Brief #2. New York: IAVI, 2004.
[3] Making Markets for Vaccines: Ideas to Action. The report of the Center for Global Development Advance Market Commitment Working Group. Washington, DC: Center for Global Development, 2005.
[4] Rockefeller Foundation. Accelerating the Development of Preventive HIV Vaccines for the World. Summary Report and Recommendations of an International Meeting. Bellagio, Italy, 1994. Available: http://www.iavi.org/about/bellagio.asp.
[5] HIV Vaccines and Microbicides Resource Tracking Working Group (AIDS Vaccine Advocacy Coalition, Alliance for Microbicide Development, IAVI, and UNAIDS). Tracking funding for preventive HIV vaccine research: estimates of annual investments and expenditures, 2000 to 2005. June, 2005.
[6] Global Forum for Health Research. Monitoring Financial Flows for Health Research. Geneva: Global Forum for Health Research, 2004.

Figure 1. Global investment in AIDS vaccine R&D in 2004 by source



Source: HIV Vaccines and Microbicides Resource Tracking Working Group, 2005.

Whereas about 48 percent of total worldwide investments in health R&D comes from the pharmaceutical industry,[7] the private sector accounts for just 10 percent of all AIDS vaccine R&D funding (see Figure 1). Commercial investment is critical to accelerating the development of an AIDS vaccine and bringing a candidate through the full R&D process to market. The private sector has unique skills, know-how, and capital required to address the scientific and logistical challenges of developing an AIDS vaccine. Innovation increasingly comes from biotechnology firms, while costly later stages of vaccine development, such as clinical testing, regulatory approval, production, and distribution, require the expertise, infrastructure, and managerial capacity of the larger pharmaceutical companies. These companies have traditionally played the leading role in translating basic research into successful products. Developing-country firms in emerging markets, already leaders in some areas of vaccine manufacturing, will become more important new sources of innovation.

Private sector officials have described several key barriers to greater investment in AIDS vaccine R&D.[8] Vaccines carry high research and development costs, particularly for the lengthy, large-scale trials required to establish efficacy. In addition to perceived scientific risks, market uncertainties are a central concern of the private sector. The largest demand for an AIDS vaccine will be in the countries that are least able to pay, and at the same time, the compelling social need for vaccines may result in significant pressure to sell an effective vaccine at a heavily discounted price. These conditions create disincentives for private investment in R&D which, if successful, would have far-reaching social and economic benefits.

1.2 Potential benefits of an Advance Market Commitment (AMC)

The CGD report argued that a properly designed and implemented advance market commitment for vaccines could have a significant impact on industry's investment decisions and thereby accelerate vaccine development and delivery. In addition to guaranteeing a substantial market for an AIDS vaccine, thus eliminating a significant cause of industry's reluctance to invest, an AMC could have several other benefits, including:

- Creating opportunities for a broad range of private sector enterprises, because donors would not make bets on specific technologies or companies;
- Rewarding development of both the first vaccine meeting technical criteria for effectiveness and second-generation vaccines;

[7] Ibid.

[8] See Batson A and Ainsworth M. Private investment in AIDS vaccine development: obstacles and solutions. Bulletin of the World Health Organization 2001; 79(8): 721-7.

- Making an AIDS vaccine available in low-income countries in Africa and Asia that bear the heaviest burden of disease while ensuring long-term access at a sustainable price;
- Allowing developing countries to choose which products they use, because donors would only pay when countries procure selected vaccines;
- Enabling donors to pay for successful outputs, not for inputs with uncertain results. Funds would only be released when a qualifying vaccine becomes available. In the meantime donor resources could be used for other initiatives to fight AIDS, improve health, and spur economic growth and development;
- Bringing a vaccine developed in the private sector to poor countries without compromising intellectual property protections.

An AMC could thus accelerate vaccine development by reducing the financial and political risks associated with AIDS vaccines and by allowing AIDS vaccines to compete more successfully with other uses of capital and research capacity. Thus, such a commitment could encourage large pharmaceutical companies to initiate or enlarge AIDS vaccine programs and to acquire promising vaccine technology developed by others. While the incentive might act most directly on large firms with the capacity to bring a vaccine to market, the enhanced prospect of investment by big pharma could in turn encourage early-stage research and development by smaller firms. Moreover, the greater chance of selling or licensing vaccine technologies to pharma could make it easier for biotechnology companies to obtain the venture capital necessary to pursue promising leads.

Although ideally an AMC would stimulate AIDS vaccine research and development in general, it could also play the more restricted but vital role of ensuring that industry develops, tests, and manufactures rapidly and at sufficient scale vaccines specifically tailored to the needs of the developing world. Particularly once the route to a useful AIDS vaccine is clearer – perhaps as soon as 2008, when results of the important Merck phase 2b trial will be available – it will be crucial to have incentives in place to drive substantial additional investments in manufacturing, should the vaccine and other related products in the pipeline prove to be successful. Although this report is primarily focused on an AMC designed to stimulate early-stage R&D, we are exploring as well the structure and benefits of a commitment with this narrower aim of scaling up vaccine production.

An AMC could also make vaccine supply more reliable by creating a large, secure market and thus ensuring that it is in companies' interests to scale up production capacity rapidly and efficiently, perhaps in collaboration with developing country manufacturing firms. An AMC could accelerate vaccine adoption, since the guarantee that the vaccine will remain available at an affordable price would encourage developing countries to adopt it.

Reaping the full benefits of an AMC would, however, require improvements in the overall vaccine system. For example, more efficient procurement by UNICEF and individual countries, better demand forecasting, and stronger in-country delivery systems would all be necessary for an AMC to achieve maximum impact. Initiatives that address these larger systemic issues are vital both to the success of an AMC and to maximizing the health benefits of an AIDS vaccine.

1.3 Key components of an AMC

For an advance market commitment to work, industry must find it both credible and sufficiently attractive to drive R&D. At the same time, AMC sponsors must be confident that they would only be obliged to purchase a vaccine that would significantly affect the course of the epidemic. Some of the salient features of an AMC, as envisioned by the CGD report, are summarized below.

- **Vaccine eligibility requirements.** The AMC sponsors would establish minimum specifications for vaccine characteristics, including efficacy, duration of protection, and usability requirements. Any vaccine meeting these pre-set terms would be eligible for purchase.
- **Price and quantity guarantee.** Sponsors would agree in advance to pay a set price per vaccinated individual, up to a maximum number of vaccine courses.
- **Subsequent low price.** Once the maximum quantity had been purchased, the developer would be obligated to continue to supply the vaccine to eligible countries at a lower agreed price, which would be set to cover the marginal costs of production.
- **Eligible countries.** The sponsors' price guarantee would apply only to sales in pre-specified countries – those with a large share of the population living in poverty and threatened by the vaccine-preventable disease.
- **Country co-payment.** Recipient countries would be free to choose among qualifying vaccines and would pay a specified minimum amount for the vaccines to qualify them for the donors' top-up. Donors could choose to make this payment on a country's behalf. Countries would procure vaccines through existing channels.
- **Legally binding contracts.** The features listed above would be codified in a set of contracts between sponsor(s) and participating companies; these contracts would be binding and enforceable legal commitments, structured to be credible to industry. The initial Framework Agreement would establish rules for competition among potential vaccine developers; at this stage, there would only be minimal obligations on the part of the signing companies. Any "winners" from the open stage would have the right to enter a bilateral contract with the sponsor, the Guarantee Agreement, which would allow the designated supplier to receive the pre-specified price for any qualified sales. Either party could pursue standard legal remedies – such as money damages and specific performance – if the other party fails to satisfy its contractual commitments.
- **Independent Assessment Committee (IAC).** This oversight body, composed of experts with backgrounds in pharmaceuticals and global public health, would ensure impartial implementation of the AMC contract. The IAC would make the final decision on whether a candidate product qualifies for the payment and would be able to relax standards on certain vaccine specifications based on the AMC objectives as set forth in the contract. Once a vaccine has been deemed to qualify for purchase, the IAC would monitor sales, use and performance of approved vaccines – and approve new vaccines under the terms of the Framework Agreement. Importantly, the IAC's operational budget – to be provided by the sponsors – must be independent, so that the sponsors are unable to influence the decisions of the committee after establishing the rules of the game. Similarly, there

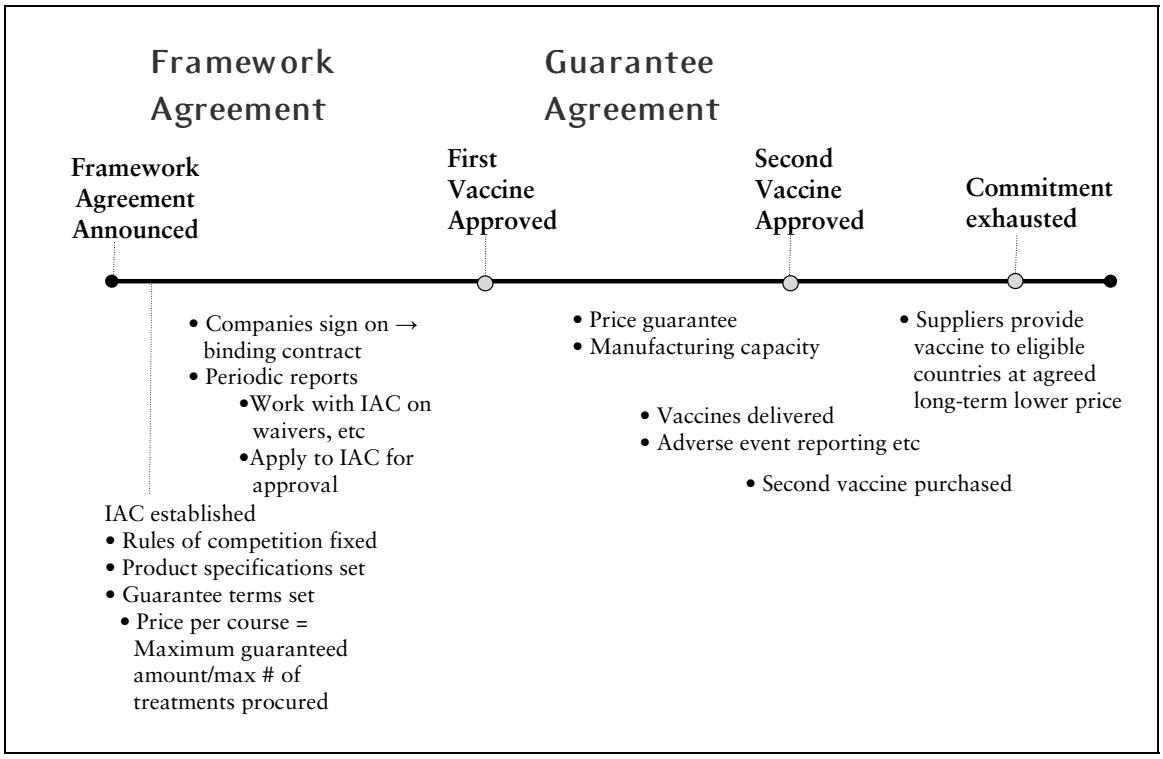
would be straightforward rules allowing the IAC to recruit new members in the case of retirement or death.

1.4 The overall AMC implementation process

Figure 2 illustrates how an AMC would be implemented over time. The steps described here follow in most respects the process presented in the CGD report but include some new features based on industry and sponsor feedback. These new features, some of which are highlighted below, are described in Chapter 2 and reflected in the Term Sheets in Annex 1.

- First, the sponsors announce a Framework Agreement, which establishes the terms of the AMC, including the vaccine eligibility requirements, the price per treatment, and the maximum number of treatments. When interested companies sign on to the Framework Agreement, it becomes a binding commitment on the sponsors. In contrast, this first contract requires little from the companies, whose only obligation is to provide periodic progress reports to the IAC. Companies may consult with the IAC, much as they do with the US Food and Drug Administration (FDA), to determine if a waiver might be granted for their product.
- Second, a company that develops a potentially qualifying product applies to the IAC for approval. If the vaccine meets the eligibility requirements laid out in the Framework Agreement, it is approved and the company becomes eligible to sign a Guarantee Agreement with the sponsors. The Guarantee Agreement requires the sponsor to pay the prespecified reward (price guarantee) for any qualified sales. Qualified sales would be restricted to those that meet criteria established in the original commitment. The quantity of vaccines to be delivered is determined by eligible country demand.
- Third, the AMC allows for second entrants to the marketplace. New vaccines must meet the eligibility requirements outlined in the Framework Agreement and be approved by the IAC. Once a new vaccine is approved, the sponsors are required to pay the second company the guaranteed price for qualifying sales of its product. The maximum quantity stipulated in the AMC is split among qualifying vaccines according to demand.
- Fourth, once the AMC is exhausted, all participating companies are required to continue supplying vaccines to eligible countries at the agreed-upon long-term price.

Figure 2. AMC implementation timeline



Annotated contracts are attached in Annex 1. The IAVI team updated and modified the Term Sheets presented in the CGD report, adapting them for the case of an AIDS vaccine. Several changes are worth noting here:

- **Generic waivers**. To ensure that the IAC process is efficient, we propose that the IAC offer generic waivers that apply to all applicants whenever possible instead of issuing waivers specific to certain vaccines, Moreover, though individual firms could consult confidentially with the IAC regarding the need for a waiver, the IAC would issue a public and general waiver without reference to individual companies or products.
- **Contract administrator.** The new Term Sheets amplify the scope of work for the contract administrator, contemplate a new secretariat function, and include some payment mechanics. These additions imply a narrower role for the IAC.
- **Independent Assessment Committee.** We have added language on how the IAC might be established and maintained and considered institutions with which it might be associated, such as the World Bank or GAVI. The new Term Sheets allow for pharmaceutical industry representation on the IAC. We also modified the name for this body from "Independent Adjudication Committee," as some felt that the latter name implied litigation.
- **Second entrants to market.** The new Term Sheets no longer require that second entrants demonstrate superiority over already qualifying products in order to be eligible to participate in the AMC. New vaccines are eligible in this model as long as they are the result of independent research (see Section 2.2).

- **Long-term price.** The long-term price set in the Framework Agreement is now eligible for waiver by the IAC. We also consider other possible approaches to setting this price (see Section 2.5).
- **Country co-payment.** The amount that countries must pay to purchase vaccines Is fixed to the long-term price, and we propose that firms be allowed to lower this price in an effort to increase market share. Together, this option and the possibility of long-term price waivers make the AMC structure more flexible in the face of uncertainty over future production costs and market conditions.
- **Supply obligation.** We define the supply obligation more precisely, tying it to demand forecasts agreed between individual firms and the AIC, and introduce more stringent provisions for enforcing this obligation.

1.5 The structure of this report

In the following chapters, we consider an AMC for AIDS vaccines in detail and discuss its implications. Chapter 2 proposes and justifies specific terms for an AIDS vaccine AMC, outlining technical specifications for vaccines, country eligibility requirements, guaranteed price and maximum quantity, and long-term price. Chapter 3 summarizes major findings from consultations with the pharmaceutical industry. Chapter 4 presents the results of our analysis of the impact and cost-effectiveness of an AMC for AIDS vaccines. Finally, Chapter 5 summarizes our major findings and outlines the most important areas for further work.

2.0 AMC terms for AIDS vaccines

This proposal adapts the CGD working group's general AMC structure to the case of AIDS vaccines and recommends specific standards and contract terms in the following areas (see Figure 3 for an overview):

- Vaccine eligibility requirements
- Provisions for second entrants
- Country eligibility
- Guaranteed price and maximum quantity
- Country co-payment and long-term price

We also introduce a number of modifications and enhancements to the contract structure to reflect further input from donors and private sector companies. These changes are also reflected in the attached Term Sheets.

2.1 Vaccine eligibility requirements

2.1.1 General considerations

Eligibility requirements in the form of technical specifications are an indispensable part of any advance purchase or advance market commitment – no sponsor can commit to paying for a product without some assurance that it can serve its intended purpose. Yet setting appropriate standards for a vaccine that does not yet exist poses substantial challenges.

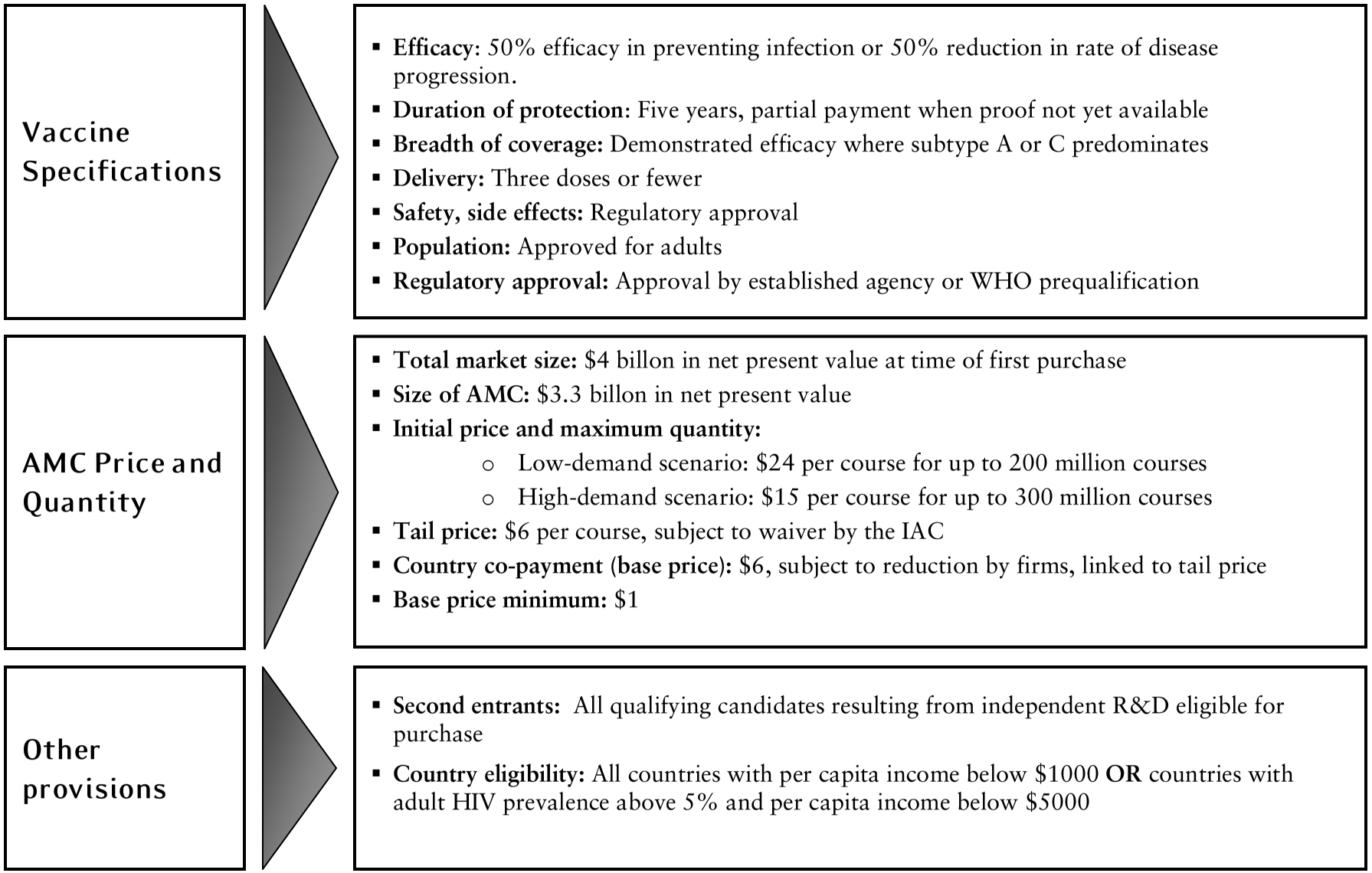
Eligibility requirements for a vaccine AMC must balance several objectives:

- The standards must be high enough that sponsors can be confident that any qualifying product will be sufficiently useful to justify their expenditure, yet not so high that developers will be deterred from investing in achieving them.
- Technical specifications must be detailed enough to give clear guidance to developers and minimize the chance that a useless product may qualify, yet flexible enough to remain relevant in the face of unanticipated scientific developments, changes in the disease environment, availability of other prevention and treatment tools, and the financial circumstances of target countries.
- Technical specifications must be measurable. The IAC must be able to determine eligibility on the basis of information it can expect to have when a vaccine is licensed. Specifications should refer to vaccine characteristics that can be measured in clinical trials of reasonable length and size.

Two features of the AMC ease the burden on the eligibility requirements to anticipate every possible pitfall:

- The AMC will require approval by an established regulatory agency such as the FDA or the EMEA and/or WHO prequalification.
- Because purchase under the AMC is contingent on demand, eligible developing countries must be willing to purchase a qualifying vaccine in order for the donor commitment to be triggered.

Figure 3. Overview of an AMC for an AIDS vaccine



2.1.2 Approach to determining vaccine eligibility requirements

In the absence of approved AIDS vaccines and experience with their use, technical specifications for an AIDS vaccine AMC must rely on four sources of information.

- **Vaccine science and current state of development.** Because no AIDS vaccine has yet been proven effective in human trials, existing candidates provide limited information on the key attributes of a vaccine. Current knowledge does suggest, however, that AIDS vaccines of different designs could offer substantially different types of benefit, necessitating alternative efficacy standards.
- **Studies of demand and acceptability.** Information about the likely demand for and acceptability of AIDS vaccines is critical for setting vaccine standards. Demand studies can directly inform the specifications by setting lower bounds on the value of some vaccine attributes, notably efficacy and characteristics related to delivery. Demand studies are also important in setting the assumptions for analyses of benefits and cost-effectiveness that will in turn be used to set other specifications.
- **Analyses of vaccine benefits and cost-effectiveness.** Estimates of vaccine benefits and cost-effectiveness derived from epidemiological and economic modeling can define levels of vaccine characteristics necessary to ensure sufficient benefits (in lives saved, disease prevented, or other costs averted) to justify the sponsors' and developing countries' expenditures. To develop our estimates, we have relied on a modified version of a spreadsheet model developed by Michael Kremer and colleagues (see Chapter 4).[9]

2.1.3 Vaccine attributes

Our proposal sets standards for several features of an AIDS vaccine (See Box 1).

Box 1. Vaccine attributes for AMC eligibility

- Efficacy
- Duration of protection
- Breadth of coverage
- Presentation and delivery characteristics (number of doses required, storage conditions, etc.)

Efficacy

AIDS vaccines might prevent infection or delay progression to clinical disease in individuals who become infected in spite of vaccination. Because these benefits are very different, we propose separate efficacy standards for vaccines of each type.

- **Vaccines that prevent infection**. Modeling studies suggest that vaccines with efficacies below 50 percent could still bring substantial benefits. In practice, however, the usefulness of low-efficacy vaccines would be limited by vaccine demand and by the potential for behavior change. A study conducted by WHO/UNAIDS/IAVI found that some countries would not use a 30-50 percent effective vaccine at all and only a limited number of East African countries would use it broadly.[10] Moreover, the benefits of low-efficacy vaccines could be greatly

[9] Berndt ER, Glennerster R, Kremer MR, et al. Advanced purchase commitments for a malaria vaccine: estimating costs and effectiveness. NBER Working Paper No. 11288, 2005.

[10] Esparza J et al. Estimation of "needs" and "probable uptake" for HIV/AIDS preventive vaccines based on possible policies and likely acceptance (a WHO/UNAIDS/IAVI study). Vaccine 2003, Vol. 21 No. 17-18: 2032-41.

reduced or even reversed by behavior change: some people may take more risks because they believe the vaccine protects them or others. Although it is difficult to know how great this risk is, evidence of increased risky behavior in developed countries since the advent of effective AIDS treatment suggests it cannot be discounted altogether.[11] *Therefore we propose a minimum of 50 percent efficacy.*

PROPOSED STANDARD FOR CLASSICAL PREVENTIVE VACCINES

50% efficacy in preventing infection

Vaccines that slow disease progression. Many of the vaccines currently in clinical trials are expected to have at best a modest effect on the rate of new infections, but they may help control the virus after initial infection, thus delaying or preventing the development of serious symptoms. This kind of vaccine benefit could be expressed in terms of an increase in the average time from infection until the onset of symptoms requiring antiretroviral therapy, equivalent to a decrease in the rate of disease progression. The main challenge posed by this standard is that the time from infection and disease is too long to be measured in clinical trials of reasonable length. It may be necessary to accept a biological marker of vaccine effect, such as viral load, as a substitute measure. *It should be left to the IAC to determine what types of proxy evidence to accept.* In practice the IAC would probably follow of the lead of established regulatory agencies on this issue.

PROPOSED STANDARD FOR VACCINES THAT DELAY DISEASE PROGRESSION

Doubling of average time between infection and disease

Duration of protection

Vaccine duration significantly affects vaccine benefits and cost-effectiveness, although the extent of this impact depends strongly on the population being vaccinated. For example, our analysis suggests that a vaccine given to 10-15 year olds must last at least five years to be cost-effective, even in high prevalence countries, because most of the risk faced by children of this age occurs many years later. On the other hand, shorter-duration vaccines could be useful in populations already at high risk. The drawbacks of short duration can be overcome by booster shots or revaccination, but these strategies may be difficult to implement in many countries and would add significantly to vaccine delivery costs. Short-lived vaccine protection also poses some of the same dangers as low-efficacy vaccines, in that people may believe they are still protected even after protection has worn off and thus take greater risks. *We conclude that the protection afforded by a vaccine must last at least five years to ensure cost-effectiveness at a global level.*

[11] Chen SY, Gibson S, Katz MH, et al. Continuing increases in sexual risk behavior and sexually transmitted diseases among men who have sex with men: San Francisco, California, 1999-2001. American Journal of Public Health 2002; 929(9): 1387-8. See also Dodds JP, Nardone A, Mercey DE, et al. Increase in high-risk sexual behaviour among homosexual men, London 1996-8: cross sectional, questionnaire study. British Medical Journal 2000; 320(7248): 1510-11.

The principal challenge that duration poses for an AMC is measurability. Conventional efficacy trials will provide only limited information about the duration of protection, at most setting a lower bound of two to three years. Longer-term follow-up will be necessary to know if duration reaches the specified minimum. *To avoid delaying adoption, we propose that vaccines that meet a minimum duration standard of two years be eligible for immediate purchase, but at less than full price. The balance would be paid retrospectively when additional data demonstrate that the desired standard (five years) had been met*. The IAC would have the right to suspend purchase of a vaccine if subsequent information reveals that protection lasts less than five years.

PROPOSED STANDARD FOR DURATION

Full payment for demonstrated five-year duration

Lower, interim payments when proof of sufficient duration not yet available

Breadth of coverage

HIV has an extremely high degree of genetic variability, and it is not clear whether it will be possible to develop a vaccine that protects against several or all strains at once. Vaccinating against the HIV subtypes most common in Africa would provide enormous social benefits and be highly cost-effective. Vaccines that protect against subtype B, on the other hand, would mostly benefit people in industrialized countries outside the scope of the AMC program. Prevalence is low in the few developing countries where subtype B is present, making use of the vaccine less cost-effective. *We therefore propose that eligible vaccines should address subtypes A or C.* The AMC cannot require precise information on breadth of coverage, which will require additional trials to establish. But it can limit eligibility to vaccines designed for and tested against the most relevant viral strains.

PROPOSED STANDARD FOR BREADTH OF PROTECTION

Demonstrated efficacy in a region where either subtype A or C predominates

Presentation and delivery characteristics

The way a vaccine is stored and delivered and the number of doses required will greatly affect its practicality and affordability in resource-poor settings. Costs of delivery will be among the most important determinants of cost-effectiveness. *To limit these costs and maximize the number of people who are fully immunized, we propose that eligible vaccines require three or fewer doses.*

It may make sense to include standards covering other, more technical aspects of vaccine presentation; these are not discussed here.

PROPOSED STANDARD FOR PRESENTATION AND DELIVERY

3 doses or fewer

Safety

It is critical that any candidate vaccine be proven safe before purchase is approved. The requirement that candidate vaccines receive regulatory approval should provide adequate assurance of safety, however, so the AMC need not set its own safety standards.

Regulatory approval

We propose two options for regulatory approval. The IAC would accept either approval by one of a specified set of established regulatory agencies, such as the FDA or the EMEA,[12] or prequalification by the WHO. Regulatory approval would not substitute for demonstration that the specific eligibilty standards (for efficacy, duration, etc.) had been met, since these standards might be higher than those required by the regulatory agencies.

PROPOSED STANDARD FOR REGULATORY APPROVAL

Approval by an established regulatory agency

or

WHO prequalification

Target populations

To be broadly useful, vaccines must be safe and effective for adolescents and perhaps also for pregnant and lactating women. But obtaining regulatory approval for use in these populations would require additional bridging trials. *Therefore we propose that vaccines be eligible for purchase when they have been approved for use in adults.*

PROPOSED STANDARD FOR TARGET POPULATIONS

Approved for adults

2.2 Provisions for second entrants

An AMC should encourage as much competition as possible, promote development of improved products, increase product diversity, and help ensure supply continuity. Opening the market creates an incentive for the lead developer to produce the best possible product in order to retain market share, while encouraging later entrants tailored to the diverse needs of eligible countries.

The CGD Advance Market Commitment Working Group proposed that later entrants be required to demonstrate superiority over already approved products. But defining and

[12] The set of approved regulatory authorities would be periodically revised as more agencies develop the necessary technical capacity. We envision that the list would eventually include agencies in the developing world.

determining "superiority" would involve the IAC in complex and potentially contentious issues, and consultations with industry have not revealed strong interest in a superiority requirement. Approved suppliers should, however, be protected against mimics or generic competitors. *We therefore recommend that all products that meet the technical specifications and result from independent R&D should be eligible to share in AMC payments.*

The desire to encourage multiple qualifying products provides an important justification for augmenting the size of the market created by the AMC (see below). Moreover, although the sponsors cannot increase the eligibility requirements once the contract has been established, they may at some point choose to create a new market guarantee to encourage the development of improved second- and third-generation vaccines. This agreement could take the form of an open-framework agreement as discussed here, or it could consist of a bilateral agreement with one of the main manufacturers.

PROPOSED STANDARD FOR SECOND ENTRANTS

All qualifying candidates resulting from independent R&D eligible for purchase

2.3 Country eligibility requirements

The core purpose of the AMC is to accelerate vaccine development and adoption by low-income countries. It may make sense to include countries, such as South Africa and Botswana, that have somewhat higher income and extremely high disease burden, as the Global Fund to Fight AIDS, TB and Malaria has done. *Thus, we follow the Vaccine Fund in restricting eligibility to countries with income per capita below $1000, but we extend eligibility to a small set of middle-income countries with very high HIV prevalence*. Resale in non-eligible countries is forbidden.

PROPOSED STANDARD FOR COUNTRY ELIGIBILITY

All countries with per capita income below $1,000

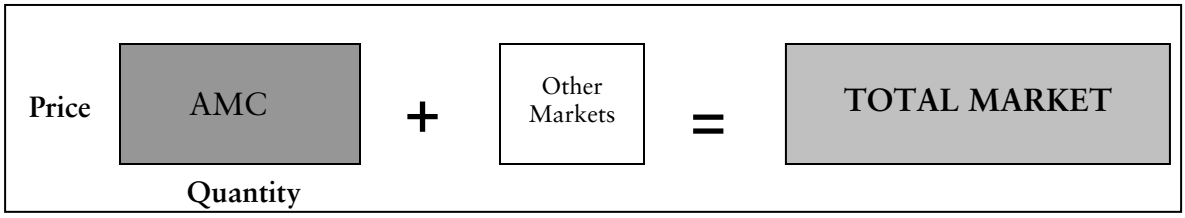
and

Countries with income below $5,000 and adult HIV prevalence above 5%

2.4 Guaranteed price and maximum quantity

We have largely followed the CGD working group's approach to setting the guaranteed price and maximum eligible quantity for the AMC. As Figure 3 illustrates, this approach involves three steps: 1) determining the necessary total market size; 2) determining the size of the AMC by subtracting expected revenues from non-eligible countries and from private purchases in eligible countries from the required total market; and 3) setting price and quantity to reach the desired net present value while ensuring that the program will last long enough to encourage innovation and ensure broad availability of the vaccine.

Figure 4. Components of total market



2.4.1 Total market size

An AMC for an AIDS vaccine should create an expected market large enough to encourage industry investment in vaccine development. One way to estimate how large this market would have to be is to look at realized revenues for existing pharmaceutical products, on the assumption that the prospect of revenues matching or exceeding those of successful products would allow AIDS vaccines to compete successfully with other possible uses of industry's investment capital. This "top-down" approach, which was adopted by the CGD Working Group, does not require detailed assumptions about industry costs and behavior; it also avoids the contentious issue of an appropriate rate of return to industry.[13]

Using data on revenues from recently developed new chemical entities (NCEs), the Working Group concluded that a total expected market of about $3.1 billion would be sufficient to motivate industry involvement in developing new vaccines. This estimate, however, does not take into account the particular scientific obstacles to AIDS vaccines, which are greater than for the average NCE or vaccine. For this reason, a larger total market size will probably be necessary to attract industry. In the absence of a systematic methodology to quantify this risk, and in anticipation of further consultation with industry and potential AMC sponsors, *we recommend increasing the total market size from the industry average of $3.1 billion to $4.0 billion to compensate for the unusually high scientific and political risks associated with development of an AIDS vaccine*. As mentioned above, the desire to encourage competition and the development of improved vaccines provides a further rationale for increasing the total market size, since the AMC payments may be shared by several qualifying products.

PROPOSED TOTAL MARKET SIZE

$4 billon in net present value at time of licensing

2.4.2 Adjustment for other revenues

An AIDS vaccine would have a significant market in high- and middle-income countries and a private market in high-prevalence poor countries. One source estimated the total

[13] In theory, one could calculate the necessary market size by estimating the required R&D expenditures, making assumptions about the probability of a candidate vaccine advancing through each stage in the process, and selecting an appropriate, risk-adjusted rate of return. In practice, however, AIDS vaccines are still at such an early stage, and the scientific uncertainties are so great, that it is very difficult to estimate how much firms will have to spend to develop a successful product. Thus we believe that this "bottom-up" approach to setting the size of an APC is not appropriate at this time for AIDS vaccines, although it may make sense for products farther along in the pipeline, when costs and risks can be assessed with greater assurance.

size of the market (in the absence of an AMC) at $1.8 billion, while another estimated $1 billion.[14] Based on this information, we assume revenues from these existing markets of approximately $1.4 billion. Because the predominant viral subtypes are different, however, products developed for the industrialized and developing worlds may differ, and separate trials will have to be conducted. To take this into account, we count only half of the projected rich-country revenues, or $0.7 billion, toward the necessary total market for a developing world vaccine. *Thus the AMC must create additional revenues of $3.3 billion to bring the total market to the desired $4 billion.*

A higher estimate of the rich world market for AIDS vaccines would reduce the size of the AMC required to stimulate private sector investment. Indeed, if the expected market is large enough, an AMC of politically feasible size may not substantially increase the attractiveness of AIDS vaccines in general to industry. Even with very high demand in the rich world, however, an AMC might still be needed to spur the development and manufacture of vaccines specifically for the developing world.[15]

PROPOSED AMC SIZE

$3.3 billon in net present value at time of first program purchase

2.4.3 Price quantity trade-off

The artificial market created by the AMC consists of purchases at a guaranteed price up to a maximum quantity; different combinations of price and quantity can achieve the same total revenues. Our view is that the balance between price and quantity should provide major benefits to the first developers while at the same time leaving sufficient incentive for subsequent products. There are several considerations in setting these parameters.

- The actual product of price and quantity must be higher than the desired net present value to compensate for discounting, since the revenues from the AMC will stretch out over several years.
- Project revenues are the appropriate measure of market size only if manufacturing costs are relatively small compared to revenues. If marginal manufacturing costs are a significant fraction of revenues, price will have to be set higher to generate sufficient operating profits. Although AIDS vaccines will probably be more expensive to produce than most existing vaccines, future manufacturing costs cannot be known until it becomes clear which technology will lead to a useful

[14] Surprisingly little data is available in the public literature on the likely market for AIDS vaccines in the developed world. These estimates, gleaned from informal sources, may be too conservative, especially in light of recent estimates of likely demand for newly developed vaccines against another sexually transmitted disease, human papillomavirus (HPV). GSK recently predicted that HPV vaccine sales could reach $4 billion a year, although other analysts have been more cautious. See N.T. Metzler, "Predicting the success of HPV vaccines," PharmExec Direct, 2005. Available: http://www.pharmexec.com.

[15] In this scenario, where expected demand in existing markets already exceeds the target for total market size and the primary purpose of an AMC is to cover the *additional* costs of producing vaccines for poor countries, the CGD approach to determining AMC size is no longer useful. But since these additional costs, covering further clinical trials and expanded manufacturing capacity, are far easier to estimate than those of overcoming large scientific challenges, the bottom-up approach used for late-stage AMCs offers a promising alternative.

vaccine. *We will assume that manufacturing costs will remain relatively low compared to revenues.*

- The choice of initial price and maximum quantity will influence incentives for ongoing innovation by shortening or lengthening the duration of the AMC and thus the opportunity for later-qualifying vaccines to capture some of the payments. *We propose that the AMC should be designed to last about 10 years to encourage second entrants.*

The number of vaccine courses that will be purchased over the first ten years will depend on how eligible countries use a vaccine, on speed of adoption, and on how rapidly vaccine supply can be scaled up. Existing analyses of demand for AIDS vaccines suggest that some high-prevalence countries will aim to vaccinate a substantial share of the adult population through mass campaigns.[16] Since it is impossible to know at this stage the extent to which vaccine production will be able to meet this potentially very large demand, we consider two scenarios that differ in the coverage of initial catch-up vaccination (see Chapter 3 for details).

PROPOSED INITIAL GUARANTEED PRICE AND MAXIMUM QUANTITY

Low-demand scenario

$24 per course for up to 200 million vaccination courses

High-demand scenario

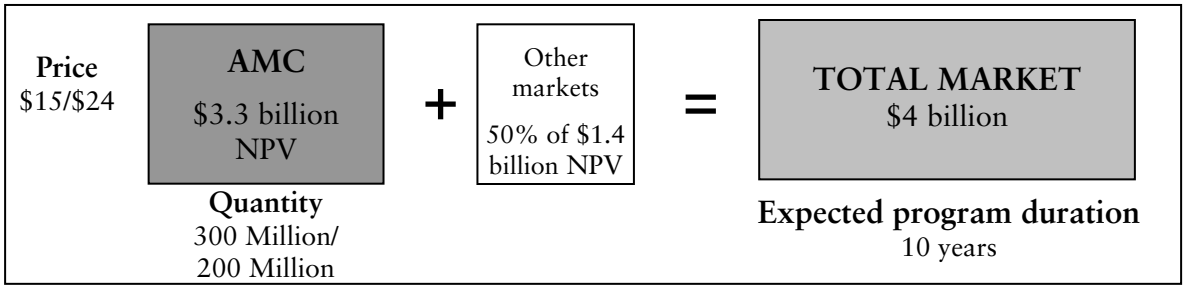
$15 per course for up to 300 million vaccination courses

In the high-demand scenario, we project that a quantity limit of 300 million vaccination courses would be reached in about in about 10 years. *Assuming a real discount rate of 8 percent, a price of $15 per course would then give the desired $3.3 billion in net present value.* In the lower demand scenario, only 200 million courses would be purchased over the first 10 years. *In this case, a price of $24 is required to bring the net present value of the commitment to a similar level, $3.4 billion.* The Term Sheets follow this second scenario.

Many firms participating in our industry consultations felt that these proposed prices were too low (see Chapter 3). This is clearly an area where further analysis and consultation will be necessary. We hope, however, that our analysis illustrates the trade-offs that must be considered in setting the guaranteed price. In particular, setting the price higher would require either increasing the total size of the commitment, accepting shorter duration (and thus less opportunity for second entrants), or revising downward the estimate of uptake.

[16] IAVI has commissioned a new study of AIDS vaccine demand in both developing and developed markets. Results are expected in mid-2006.

Figure 5. Price, quantity and total market for an AIDS vaccine AMC



2.5 Country co-payment and long-term price

2.5.1 Country co-payment

Recipient countries would pay a specified amount for all the vaccines they buy. This co-payment (called the "base price" in the Term Sheets) would build country ownership and ensure that only useful vaccines are purchased. Development partners (but not suppliers) would be free to assist with these payments, which could otherwise constitute a substantial barrier to participation by the poorest countries.

Ideally the *country co-payment should be close to the marginal manufacturing cost of the vaccine and thus to the long-term price under the AMC*. But we cannot know now with any precision what future AIDS vaccines will cost to produce. To accommodate this uncertainty, we propose two new mechanisms that would allow the co-payment and the long-term price, which we formally link to one another, to be changed in light of actual costs and market conditions. First, we propose that firms be permitted to lower the co-payment for their vaccines as long as it remains above a specified minimum. Suppliers would not be allowed to raise the base price once they had lowered it. Moreover, firms that lowered the co-payment would be required to reduce the long-term price by the same amount, thereby committing to supplying their vaccine at this new, lower price after the AMC had been exhausted.[17] Second, we allow firms to petition the IAC for an increase in the long-term price (and thus the co-payment) if they can show that their vaccine cannot be manufactured for the agreed price (see below). For more detail on these modifications to the AMC structure, see the Term Sheets (Annex 1).

In addition to giving the AMC greater flexibility in the face of uncertainty, these mechanisms would make price competition possible (firms could lower prices to retain or increase market share, much as they would in natural markets), giving firms additional incentive to drive down costs. Developing countries, for their part, would be able to

[17] The Center for Global Development AMC proposal explicitly prohibited firms from paying the base price on behalf of purchasing countries, to prevent them from gaining market share (and high-price payments) at no cost to themselves and subverting an important element of the AMC structure. Three features of our proposal guard against this danger. First, firms cannot lower the base price below the specified minimum, which would remain a significant expense to eligible countries. Second, the total price received by suppliers would fall when they lowered the base price (the top-up by donors would remain the same). Most importantly, the obligation to supply the vaccine after the end of the AMC at the new, lower price should deter firms from setting the base price below cost, as long as they believe they will be held to this obligation. The revised Term Sheets accompanying this report define the supply obligation more precisely and introduce several more stringent provisions for enforcing it.

consider long-term price in deciding which vaccine to purchase. *We propose a country co-payment of $6 per course of treatment (equal to the proposed long-term price) and a base price minimum of $1.*

PROPOSED CO-PAYMENT OR BASE PRICE

$6 per course of vaccination

PROPOSED BASE PRICE MINIMUM

$1 per course of vaccination

2.5.2 Long-term price

One of the most important features of the AMC as envisioned by the CGD working group is two-stage pricing. In return for receiving the sponsor-subsidized initial guaranteed price, participating firms commit to providing the vaccine to eligible countries thereafter at a lower price. This commitment helps ensure the new vaccine will be financially sustainable for developing countries, which in turn encourages adoption.

In theory, the long-term price (called the "ongoing supply price ceiling" in the Term Sheets) should be set at or close to the long-term marginal cost of production to ensure that the optimal quantity of vaccine is purchased and used. Since firms are assumed to have recouped their investment from the high-price AMC payments, the long-term price does not need to include a mark-up to recover these sunk costs.

The challenge in setting this price is that these manufacturing costs cannot be known at the time the AMC agreement is created. *We propose, therefore, that the long-term price be set at a level determined by cost-effectiveness and long-term affordability to low-income countries, consistent with the best available information on likely manufacturing costs. We suggest a price of $6 as a reasonable starting point for further discussion of this difficult issue among industry, potential sponsors, and developing countries*. Although this amount is many times higher than the cost of manufacturing most existing vaccines in broad use in developing countries, it is low enough to ensure that an AIDS vaccine (and an AIDS vaccine AMC) would remain highly cost-effective (see Chapter 4).

Although setting the long-term price in advance creates additional risk for firms, since they must decide whether it will be possible to manufacture a particular candidate vaccine at this price, it creates a strong incentive to consider affordability along with other product characteristics in choosing among technologies and candidates. In a sense, when long-term price is specified in the contract, manufacturing cost becomes another technical specification that firms must aim to achieve. *In order to preserve flexibility, and to avoid blocking altogether development of promising candidates that may have trouble meeting this standard, we propose that the long-term price be subject to waiver by the IAC in the same way as the technical specifications*.[18]

[18] Waivers of the long-term price would not be automatic: firms would have to demonstrate that the increased cost was outweighed by additional benefits, such as efficacy exceeding the specified minimum. Moreover, a long-term price waiver granted by the IAC to one firm would in general apply to all firms. Other firms with

An alternative would be to set the long-term price after licensure, at marginal manufacturing cost (plus a small mark-up), on the basis of the manufacturer's data. Although this approach would guarantee that suppliers would not be obligated to provide vaccine at below cost, it would greatly weaken industry's incentive to choose affordable vaccine technologies and invest in reducing manufacturing costs. The AMC could also adopt a hybrid approach, setting long-term price at cost-plus, subject to a ceiling determined by cost-effectiveness and affordability. The CGD working group chose this option.

2.5.3 Waiver of long-term supply commitment

The requirement that suppliers who benefit from AMC payments continue to provide vaccine at the long-term price is critical for sustaining vaccination programs in low-income countries. But if several products qualify and share in AMC sales, it makes sense to relax this requirement. Some suppliers, especially those that enter the market late, may receive only a fraction of the AMC payments and thus have little chance of recouping their development costs. *To provide some relief to these firms and to increase the incentive for development of second-generation products, we propose that suppliers be permitted to charge a somewhat higher long-term price until their total sales reach a pre-determined fraction of the total AMC size*. In addition, on-going demand for some qualifying products may be too low to justify maintaining expensive supply capacity. *Thus we propose that the long-term supply obligation be waived for products whose market share falls below 10 percent,*[19] *or whose actual sales are far below the sales forecast by the IAC.*[20] (See the Term Sheets for details.)

2.6 Summary

In this chapter we have outlined our proposed terms for an AIDS vaccine AMC. Although these choices will of course be revisited before an AMC is established, we hope that this exercise has illustrated practical and defensible approaches to establishing the terms of an AMC and highlighted some key issues that will require further examination.

We conclude in particular that plausible vaccine eligibility requirements can be set even in the absence of much information about the attributes of future AIDS vaccines, although our analysis raises previously-neglected issues about the kinds of information that will be available to the IAC at the time of licensing. We follow the CGD working group in adopting a "top-down" approach to determining the size of an AMC, with an adjustment for the unusually high scientific risk. We set the guaranteed price and maximum quantity to ensure that the commitment will last about ten years, using our analysis of likely vaccine uptake to relate quantity to duration. Finally, we set the long-term price on the basis of affordability and cost-effectiveness but make it subject to waiver by the IAC and downward revision by firms.

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lower costs would be free to charge the original long-term price, or to lower it together with the country co-payment, using the new mechanism described in the preceding section.

[19] A firm with small market share might be required to continue to supply its vaccines if it were the only suitable product for one or more eligible countries.

[20] As an important step toward defining a realistic and enforceable supply obligation, we propose that the IAC and suppliers work together to project demand for qualifying vaccines.

3.0 Feedback from industry

As part of developing a draft proposal for an AIDS vaccine AMC, the IAVI team consulted with representatives of a potential AMC sponsors (DfID and UK Treasury) and with officials from industry. These consultations allowed the team to solicit input and feedback and helped to shape the proposal outlined here. This chapter describes the team's approach to industry consultations, provides an overview of what the team heard from industry, and concludes with areas that require further discussion as the G8 countries move towards making the AMC idea a reality.

3.1 Methodology for industry consultations

3.1.1 Objectives

The industry consults were carried out in partnership with the Malaria Vaccine Institute (MVI) and BIO Ventures for Global Health (BVGH). The group agreed on the following objectives:

- Raising awareness of the general concept and basic principles of an AMC;
- Soliciting specific feedback on AMC proposals for AIDS and malaria vaccines;
- Encouraging industry to participate in AMCs for AIDS and malaria vaccines.

3.1.2 Approach

The group considered a range of approaches and consulted the CGD team that carried out similar consultations two years ago. Among the approaches considered were one-on-one meetings with key firms, group conversations with officials from several firms, and opportunistic presentations at existing events.

In the end, the group relied primarily on meetings with individual firms. The IAVI team, in some cases accompanied by representatives from MVI and BVGH, met individually with eight firms. Most of these meetings were conducted in person. In addition, BVGH arranged for a group meeting with members of its board, representing a further six firms (Annex 2).

3.1.3 Selection of firms

In consultation with key stakeholders, the IAVI team chose firms on the basis of their involvement in the AIDS field and their knowledge of or interest in AMCs. The team was careful to ensure that the selected firms represented the different segments of the pharmaceutical industry: large pharmaceutical companies, medium and large biotech firms, and emerging country manufacturers. The IAVI team sought to include individuals with decision-making authority from each firm. Participants included presidents, CEOs, and chairmen; vice presidents for business development, marketing, and government affairs; and science directors.

Table 1. Overview of Firms Consulted

Type of firm	Number of firms	Venue
Large pharmaceutical companies ▪ GSK-BIO ▪ Sanofi-Pasteur	2	In-person
Biotech companies ▪ Bavarian Nordic ▪ Chiron ▪ Crucell ▪ Targeted Genetics	4	In-person and video conference
BVGH Board Members and Business Advisors ▪ Nektar Therapeutics ▪ Acambis ▪ SG Cowen ▪ Alloy Ventures ▪ Avant Immunotherapeutics ▪ AlphaVax	6	In-person and video conference
Emerging pharmaceutical companies ▪ FIOCRUZ ▪ Serum Institute	2	Telephone calls
Total	**14**	

3.1.4 Evolving discussion of AIDS AMC proposal

The industry consultations evolved into an on-going conversation between the IAVI/MVI/BVGH group and industry. All the meetings followed a similar structure – presentations from IAVI and MVI followed by questions and comments. Each meeting advanced the IAVI team's thinking and led to changes in the draft proposal, and in turn, the meetings helped further industry's understanding of AMCs. During the consultative process, it became clear that even though many company officials had heard of AMCs, or had even participated in meetings on the topic, many still harbored misconceptions concerning their purpose and structure. The group spent considerable time reviewing some of the basic concepts as well as the nuances of the AMC concept.

3.2 Common themes

The following section presents findings from the industry consultations in the following thematic areas:

- Vaccine specifications
- Total market size
- Guaranteed price
- Long-term price
- Second entrants to market
- Independent Assessment Committee
- Likely effect on industry behavior

In this summary, we have sought to capture industry's feedback as faithfully as possible without inserting our perspective.

3.2.1 Vaccine specifications

Most of the companies interviewed were comfortable with the proposed standards for AIDS vaccines as well as the methodology for defining them, given current scientific uncertainties. Participants noted that industry uses product profiles to guide its own development work. One biotech firm, however, presented a provocative alternative to including vaccine specifications in the AMC, suggesting that the acceptability of a vaccine could be left entirely to the market (subject to conventional regulatory approval).

Box 2. Draft specifications for an AIDS vaccine

- **Efficacy**: 50% efficacy in preventing infection or 50% reduction in rate of disease progression.
- **Duration of protection**: Full payment for 5 years
- **Breadth of coverage:** Demonstrated efficacy in populations where subtype A or C predominates
- **Delivery:** 3 doses or fewer
- **Safety, side effects:** Regulatory approval
- **Population:** Approved for adults

Below are some responses to specific vaccine standards:

- **Efficacy**. All were comfortable with 50 percent efficacy as a minimum but agreed that developers should strive for higher efficacy. One firm objected to the inclusion of vaccines that slow disease progression, although the reason for the objection was not clear.
- **Duration of protection**. All recognized the importance of duration for an AIDS vaccine and thought five years seemed a reasonable standard. Some participants, however, were uncomfortable with the suggestion of partial payment for a vaccine that could not immediately demonstrate five years duration, fearing that this approach would introduce delays and unnecessary complexity.
- **Safety, side effects**. Most agreed that it is best to handle safety and side effects by requiring regulatory approval, but participants disagreed over whose approval should be required. One emerging market manufacturer and one large pharmaceutical company strongly opposed requiring WHO prequalification. One firm explained that since the WHO already relies on decisions reached by established regulatory agencies such as the FDA and the EMEA, it would be simpler and faster to rely directly on approval by these agencies. The firm asserted that WHO does not have the resources to process prequalification applications efficiently, so the process can take as long as two to three years. Some firms expressed concern over the idea that requirements for AMC qualification could differ from (and exceed) requirements for regulatory approval.

There was some discussion of how the IAC would handle trade-offs among vaccine specifications and of the process for obtaining IAC waivers. All companies welcomed the concept of general waivers and the idea that firms would be able to discuss potential waivers with the IAC during the development process.

3.2.2 Total market size and estimate for AMC

The proposed size of the AMC was one of the most hotly discussed topics at the meetings with industry. There was universal agreement that the AMC should be large enough to pull more than one developer. Indeed, a common refrain was *"the larger the market, the more new entrants it will attract."*

But agreement ended there: no clear consensus emerged on the proposed $3.3 billion market size or on the methodology for determining it. Opinion on whether a $3.3 billion AMC would change industry's behavior was divided but did not depend in an obvious way on the nature or size of the firm. Several biotech firms and an emerging manufacturer were comfortable with the $3.3 billion proposal and believed it would be big enough to motivate big pharma to enter the marketplace.

One participant commented that a total market size of $400-500 million per year (roughly equivalent to the proposed $3.3 billion in net present value) would attract many companies that are not currently in the vaccine business. If the market were two to three times higher, this company argued, it could also drive the formation of new biotech companies focused on HIV vaccines. On the other hand, several biotech officials thought that $3.3 billion was almost certainly too low, arguing that the vaccine market has changed. One cited the case of the pneumococcal vaccine Prevnar, which has had about $4 billion in sales in just the past five years. One respondent from big pharma asserted that $3.3 billion would attract no firms, but an AMC of $7-8 billion might bring in three or four companies.

A few participants suggested an AMC of this size might actually be too large and could distort the vaccine market.

<u>Option to increase AMC</u>
Some participants suggested that the IAC have the ability to increase the amount of the AMC if very few developers are signing up to the Framework Agreement. Others suggested that sponsors may need to "reload" the AMC when the original commitment is exhausted in order to drive development of improved vaccines.

<u>Methodology to calculate total market and AMC size</u>
The discussion on methodology entered into the industry consults at a later stage. As a result, the IAVI team received relatively little feedback in this area. But some of the biotechs expressed doubt that the CGD's top-down approach to sizing the market would lead to an adequate estimate. One firm argued that a risk-adjusted analysis by disease should be done, in order to estimate the minimum size necessary to ensure that firms would recoup their investments. The same representative pointed out that firms are going to do their own calculations using a risk-adjusted approach before deciding to enter into an AMC. On the other hand, a large pharmaceutical company expressed comfort with an approach based on annual revenues and did not disagree with CGD's rule of thumb of $500 million in peak sales.

Several firms objected to consideration of revenues from markets outside the eligible countries in determining AMC size on the grounds that different products would be

required for the different markets. This position may also reflect concern that industry will be forced to use rich market revenues to subsidize production for poor countries.

3.2.3 Guaranteed price

The guaranteed price was the most discussed topic in the industry consultations. Almost all companies interviewed stated that the original proposed price of $15 per course of treatment was too low and would pose a significant barrier to industry participation. (There was little feedback on the revised price of $24.) The most significant concern about the guaranteed price was that it might not allow a sufficient margin over manufacturing costs: all firms anticipated that AIDS vaccines will require new and expensive technology, which will have a major impact on manufacturing cost.

When asked what would be a reasonable price for a course of vaccination, many firms said it would be too difficult to set the price this far in advance but offered other vaccine prices as a point of comparison. One biotech firm, for instance, stated that it costs $15 to produce a single dose of its smallpox vaccine; a second firm said it costs approximately $7 per dose to manufacture a rabies vaccine. A third biotech executive stated that one could extrapolate what the cost might be for an AIDS vaccine based on existing technology, with the recognition that one may realize some cost reductions with economies of scale. But he added, as did many respondents, that an AIDS vaccine would likely require new technology, making this kind of estimate less relevant.

Others tried to back into an appropriate price by outlining some of the costs, stating that it costs from $30-$100 million to conduct a Phase III trial and approximately $50-$100 million to build a plant producing around 50 million doses annually. R&D costs would have to be considered as well.

An emerging pharmaceutical company representative indicated that $24/course might be a reasonable price for a vaccine with efficacy higher than 50 percent. A biotech firm executive wondered if her firm would be able to recoup costs even at this higher price; she wanted assurance that if her firm did its best to drive down costs and still could not meet the price, they would still earn a decent return on investment.

In general, firms were uncomfortable with setting a price so far in advance, given the absence of meaningful information on future manufacturing costs. Two companies stated bluntly that setting a price in the Framework Agreement presented a problem for them and would be a disincentive to participation in an AMC. A representative of a biotech firm suggested that rather than setting the price up-front in the Framework Agreement, AMC sponsors should specify it later, when there was more information. But he recognized that donors may not be comfortable with this level of uncertainty.

One representative of a large pharmaceutical company, citing the firm's experience with ARVs, raised the concern that a price set in a Framework Agreement for an AMC would prove politically difficult to raise later, even if new information on costs emerged. The representative argued that public awareness of the AMC price could also compromise the firm's ability to charge a higher price outside the AMC, particularly in middle-income countries. When the IAVI team explained that the guaranteed price in the Framework Agreement is intended to be a "floor" price and that it is not meant to limit what firms

could charge in other markets, her response was that real world experience suggested that the price would be perceived as a ceiling.

3.2.4 Long-term price and supply commitment

For some, setting the long-term or "tail" price was the most difficult aspect of the AMC. All the companies interviewed agreed with the purpose and intent of a tail price. Indeed, many said that the tail price should send a message to industry to choose an appropriate technology to produce an AIDS vaccine cheaply. But there was considerable disagreement on how to set this price.

Box 3. Proposed long-term price

Strategies to set long-term price

1. Set price compatible with sustainability, treat as additional target for developers
2. Determine price after development on cost-plus basis
3. Hybrid: cost-plus with ceiling

Proposed long-term price

$6.00 per course of vaccination

As with the guaranteed price, the major challenge in setting the long-term price is estimating future manufacturing costs. The IAVI team proposed two strategies to address this constraint, as well as a hybrid option (see Box 3). Several biotech officials said that rather than a cost-plus system that would require them to disclose costs, they preferred the idea of setting a reasonable long-term price in advance. These firms explained that most companies are not comfortable revealing cost information to outside parties, particularly when they are trying to sell identical products in developed-world markets. Two other firms said they would prefer the hybrid option – cost-plus with ceiling – as a way to address future unknowns. Only one firm, a developing world manufacturer, said it felt comfortable with the cost-plus option, explaining that they already employ this approach with a major customer.

Almost all companies felt that the original proposed long-term price, $1, was too low. There was some indication that even the $6 price could be too low to cover costs, although participants also acknowledged that $6 might prove too high for many developing countries. Also, several firms – pharmaceutical and biotech alike – requested some flexibility in the obligation to continue supplying at the long-term price. Their concern was that they could be locked into maintaining expensive manufacturing capacity even if demand were very low. In response to this concern, the IAVI team modified the terms of the proposed AMC to waive the on-going supply requirement for firms with only a small share of the market (see section 2.5).

3.2.5 Other AMC provisions

Second qualifiers

All the companies approved of the goal of fostering competition. They agreed with that proposal's approach to second-generation vaccines would send an important signal to industry and provide an incentive for continuing improvement of AIDS vaccine technology. Nonetheless, some firms – a biotech and an emerging pharmaceutical firm – warned that the realities of the marketplace, particularly the large budgets for marketing and sales at the disposal of big pharma, might make it difficult for even

Box 4. Second Qualifiers

All qualifying candidates resulting from independent R&D eligible for purchase

superior second entrants to displace the first vaccine to reach market. They argued that the creation of better vaccines was a crucial issue and that the AMC needed to include mechanisms for driving continuing innovation.

Country Eligibility

All companies interviewed agreed that the AMC price subsidies should be available to developing countries only and supported the GAVI eligibility criteria in general terms. There was, however, some disagreement on whether to allow the high-prevalence middle-income countries such as Botswana and South Africa to participate. One participant asked whether the IAVI team considered including Brazil, Thailand and India. (India would be included according to the proposed eligibility standards; Brazil and Thailand would be above the income cut-off.)

Box 5. Country Eligibility

All countries with per capita income below $1,000 and countries with income below $5,000 and adult HIV prevalence above 5%

3.2.6 Independent Assessment Committee

The discussion on the IAC centered on its credibility and composition and on whether it would introduce unacceptable delays.

Credibility

Many firms stated that to be credible, the IAC should not be affiliated with a government or WHO and should be well-insulated from the political process. One biotech firm described its negative experience in contracting to produce smallpox vaccines for the US government, which apparently reneged on the purchase after the firm had invested in manufacturing capacity. This participant added that even though he recognized that the AMC permits developers to take government to courts, he did not want to be put in the position of having to sue the US government. Many liked the idea of an intermediary like the World Bank being responsible for collecting promised funds from governments.

Composition

Participants insisted that the IAC include industry expertise from the scientific, business development and senior management areas.

Decision-making process

Many company officials were concerned that the IAC would not reach decisions in a timely manner and emphasized that delays could be very costly to firms. One suggested that the committee be obligated to make decisions within a certain time. Others worried about handling a new bureaucracy with untested and unfamiliar procedures, explaining that agencies like the FDA, for all their flaws, were well understood by industry. Some of this discussion may have been influenced by misconceptions about the proposed scope of the IAC's responsibilities.

3.2.7 Other issues

Manufacturing capacity to meet worldwide demand

Many firms raised the issue of establishing sufficient manufacturing capacity to meet worldwide demand. Five firms said they believed few companies would have the capacity to meet potential demand for an AIDS vaccine. One referred to GSK's struggle to keep

pace with demand for its oral polio vaccine. Another said it would require four to six facilities dedicated to AIDS vaccines to meet demand. Two firms – a biotech and an emerging pharmaceutical company – suggested creating mechanisms in the AMC to encourage "technology-sharing" as a means to spread the supply burden among multiple producers. The developers would be compensated for the technology through royalties, payments, or a reward.

One firm suggested that the supply obligation of each firm with a qualifying product be negotiated in advance. This provision would give firms some protection from criticism if they were not immediately able to meet all demand.

Better estimates of demand

Several companies raised the need for better data on demand for an AIDS vaccine, since the AMC would not include a quantity guarantee. They argued that the private sector is comfortable with letting the market determine demand but needs high-quality modeling in order to have confidence in market behavior.

One large firm described recent experiences to highlight the importance of reliable demand information: in one case, the firm invested in production capacity for a new vaccine, but it received no orders for five years because of slow public sector decision-making. In another case, the firm endured delays as GAVI decided whether to purchase its vaccine. This company said that better tools are needed to align production and demand efficiently. It also lobbied for longer purchase contracts with GAVI, lasting as long as five to seven years, arguing that greater certainty about volume would lead to much lower prices.

Definition of market

Some participants challenged the contention that an AMC would create a true market for vaccines in developing countries. One biotech pointed out that the artificial market created by an AMC would differ from normal markets in that firms would not be able to compete on the basis of price. This would increase risk because firms faced with a superior product would not be able to preserve some market share by lowering their prices.

A large pharmaceutical company representative applauded the attempt to simulate the dynamics of the marketplace but stressed that markets in Africa are very different from those in the developed world, in part because decisions are made by governments and donors.

Appropriateness of an AMC for late-stage products

One large pharmaceutical firm was adamant that AMCs were not appropriate for late-stage products such as rotavirus and pneumococcal vaccines. The main reason seemed to be that these products were close to market and that shifting responsibility for purchase from GAVI and other existing mechanisms to an AMC would result in costly delay. A biotech representative agreed that AMCs were more appropriate for early-stage products. He expressed concern about the World Bank's proposal in Paris to do a pilot for AMCs with late-stage products and worried that AIDS and malaria vaccines could be left out.

3.2.8 An AMC's potential impact on industry behavior

In addition to soliciting feedback on the AIDS AMC proposal, the IAVI team explored how an AMC might change the behavior of different segments of industry. Most agreed that sponsors should structure an AMC to motivate big pharma because only it has the manufacturing capacity and ability to bring a product to market. Moreover, motivating big pharma would in turn bring in other segments of the industry: bio-techs would start projects with the prospect of selling their technology to big pharma, while emerging pharmaceutical firms might participate as licensed producers of eligible vaccines.

Although all firms stated the AMC should be targeted primarily at big pharma, there was less agreement on how successful an AMC would be in changing big pharma's behavior. Some firms already involved in AIDS vaccines, especially the larger ones, insisted that they were already doing all they could and thus would not change their level of effort in response to an AMC. These firms argued that their work on AIDS vaccines was limited by the scientific challenges rather than the size of the expected market, and that until there is proof of concept, there is no easy way to accelerate the process. When pressed, some of these participants acknowledged that the prospect of a larger market might affect their decisions on resource allocation, at least at the margin. A biotech executive said that an AMC would only motivate pharmaceutical companies that are already working on AIDS vaccines because others do not fully appreciate or comprehend the peculiarities of the field.

Most of the biotechs said an AMC would motivate them to initiate or to scale-up AIDS R&D, with the knowledge they could receive funding from a large pharmaceutical firm. One participant mentioned the growing reliance of big pharma on biotechs for new technology. Another described the large pharmaceutical companies as spiders sitting at the center of webs, making strategic alliances with multiple biotech firms in order to keep their options open as long as possible. He explained that they prefer not to commit to a product until it reaches later stages of clinical trials. As a result, biotechs believe it is likely that a large pharmaceutical company would wait to acquire one of the biotech firms until it has demonstrated promising technology for an AIDS vaccine.

Another biotech executive remarked that the dynamics of the marketplace have changed in the last decade and that push is no longer sufficient. In particular, he argued, pull is needed to accelerate licensing and production. Finally, a representative of one of the large pharmaceutical companies said an AMC would address some of these weak links in the development process in three ways: by increasing the efficiency of the hand-off between large pharmaceutical firms and biotechs, by accelerating progress after the proof of concept stage, and by accelerating and streamlining preparation for production.

3.3 Summary of industry feedback

Response was generally quite positive, both to the general concept and to many of the specifics of the proposal. Many firms appeared to engage seriously with the concept of an AMC and seemed eager to influence the final form it might take. Many said the IAVI proposal represented significant progress toward an initiative that industry could support.

The single greatest issue, raised by almost all firms, is that of prices and the mechanisms for setting them. Firms are uncomfortable with the proposed prices, which they see as too low, and with the general concept of setting these prices in advance (by mechanisms that bear little resemblance to those with which they are familiar). This discomfort is in turn driven primarily by a widely shared expectation that manufacturing costs for an AIDS vaccine will be much higher than those for traditional vaccines and could be high enough to substantially shrink (or even eliminate) profit at the proposed guaranteed price.

Opinions on the likely impact of an AIDS vaccine AMC differed. Some firms thought it would motivate increased R&D, especially on the part of biotechs; others insisted that progress was largely limited by scientific difficulties and thus would not be accelerated significantly by an AMC.

4.0 The impact and cost-effectiveness of an AIDS vaccine AMC

In this Chapter, we consider the potential social benefits and cost-effectiveness of an advance market commitment for AIDS vaccines. The goal of an AMC would be to hasten the development and adoption of an AIDS vaccine by stimulating the involvement of the private sector in vaccine research and development, encouraging the rapid expansion of manufacturing capacity, and ensuring affordable supply to developing countries. Its ultimate benefits would be the millions of lives that could be saved or extended by a vaccine.

Our analysis has three aims. First, it provides a preliminary – and conservative – estimate of the likely benefits, in infections averted and disability-adjusted life-years (DALYs) saved, of widespread use of AIDS vaccines in the developing world. IAVI and The Futures Group International have begun a more comprehensive analysis of vaccine impact; preliminary findings are already available (see Section 4.6); more detailed results are expected later this year. Second, it allows potential sponsors to compare the value of an AMC with that of other public health investments by weighing the benefits of an AIDS vaccine AMC against its costs. Finally, by examining how benefits and cost-effectiveness depend on vaccine characteristics, this analysis informs our discussion of minimum vaccine specifications, presented in Chapter 2.

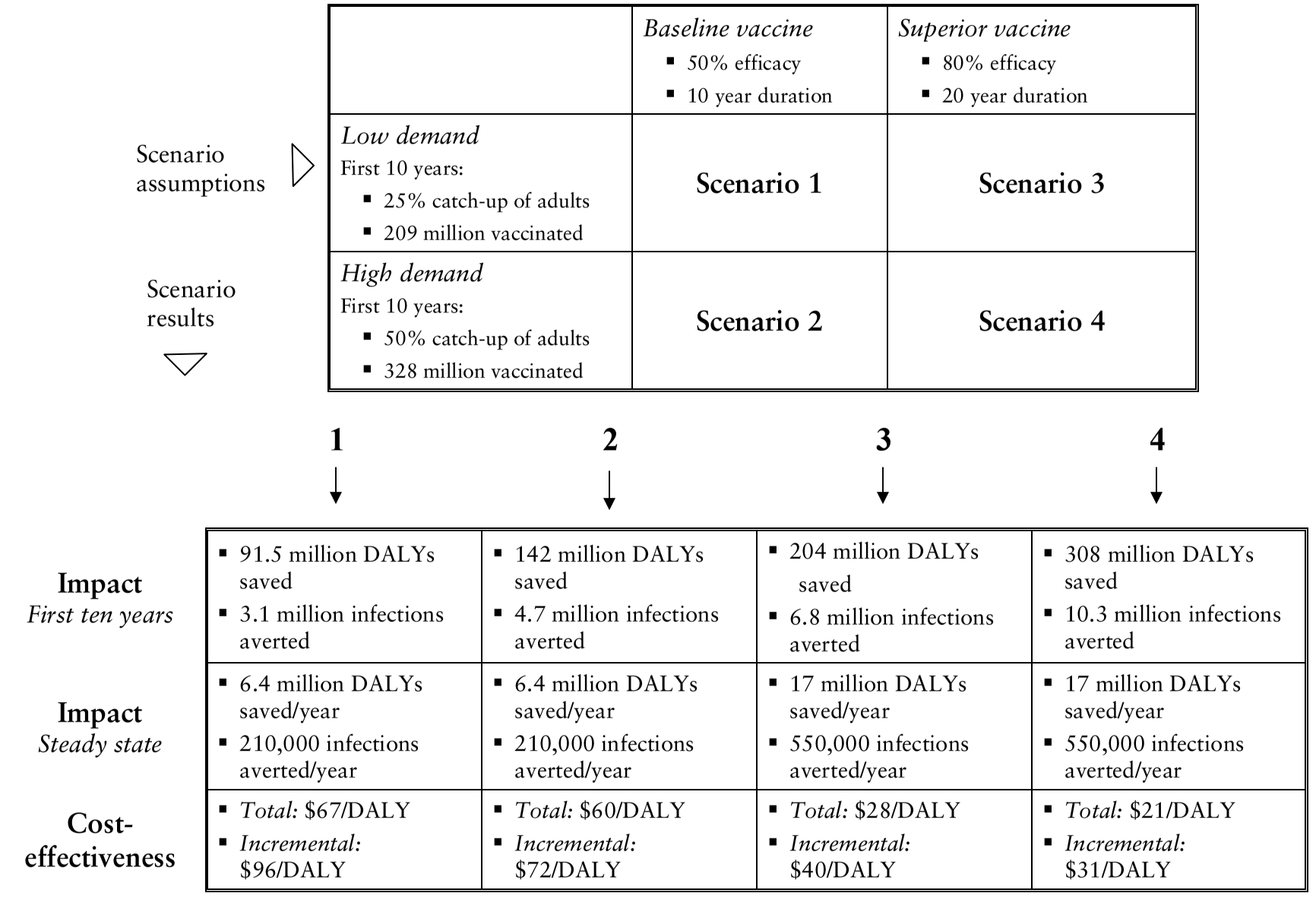
It is worth pointing out as well what our analysis does not do. It does not model the effect of an AMC on private sector investment in AIDS vaccines and thus on the time until a useful vaccine is available. It also does not examine how the expansion of vaccine supply and the rate of adoption by eligible countries depend on the existence and terms of an AMC. We explain in the Introduction why an AMC is likely to advance both development and adoption – in this section we estimate the resulting benefits while considering how they would depend on the size of this advance.

The impact of an AIDS vaccine will vary greatly with the nature of the vaccine, the way it is used, and the epidemic context at the time it is introduced. We will focus on four simple scenarios:

1. **Baseline Vaccine**: Vaccine with characteristics (50 percent efficacy and 10-year duration) close to the proposed minimum standards, modest uptake.
2. **Baseline Vaccine, High Demand**: Baseline vaccine, broader use during the first years of the program.
3. **Superior Vaccine**: Vaccine with 80 percent efficacy and 20 year duration, demand as in Scenario 1.
4. **Superior Vaccine, High Demand**: Vaccine of Scenario 3, used as in Scenario 2.

In the following section, we outline our approach to modeling vaccine benefits and our assumptions concerning vaccine use and adoption. We then present results for the four scenarios and explore in a preliminary fashion how these findings might be modified to incorporate disease-modifying vaccines and widespread antiretroviral treatment. After considering the sensitivity of our results to a few critical variables, we summarize the main lessons from our analysis.

Figure 6. Overview of modeling exercise



4.1 Approach and assumptions

4.1.1 The model

We estimate benefits and cost-effectiveness using a spreadsheet model developed for this purpose by Michael Kremer and his colleagues, modified to capture the particular features of HIV/AIDS, AIDS vaccines, and likely AIDS vaccination strategies. Two features of the model are worth highlighting here.

- **Only direct benefits considered**. The model calculates the benefits of a vaccine by adding up disease and deaths averted in people who receive the vaccine. It does not incorporate the indirect benefits of vaccination stemming from reduced transmission, an effect sometimes called "herd immunity." Although these secondary effects are potentially very large, and could in some circumstances dwarf the direct benefits, they vary greatly with the stage and nature of the epidemic, and their estimation would require numerous additional assumptions and the use of more complex and less transparent models.
- **Constant background burden of disease**. The total burden of HIV/AIDS – and its regional distribution – are static inputs to the model and thus do not change over the period considered. We have modeled vaccine impact against a projected background burden of HIV/AIDS in 2025, derived from a recently developed UNAIDS baseline scenario. In this scenario, the epidemics in Africa and Latin America remain more or less as they are today, The epidemics in Asia and Eastern Europe grow, but only modestly: the catastrophic "next wave" of HIV that some fear does not materialize. Adult prevalence in India, for example, rises only to 1.4 percent, while prevalence in China remains below 1 percent. In this sense the UNAIDS scenario can be considered optimistic (and our estimates of vaccine benefits conservative); on the other hand, the assumption that prevention efforts fail to bring prevalence down in the most affected parts of Africa must be considered pessimistic.[21]

For comparison, we present results using 2000 WHO estimates of AIDS burden and current population numbers.

4.1.2 Vaccination strategy and adoption

There has been no comprehensive study of AIDS vaccine demand. The most complete study to date, however, suggests that low and high-prevalence countries would use partially effective vaccines quite differently.[22] On the basis of this and other work, we assume that countries with low-prevalence epidemics will focus on vaccinating high-risk individuals,

[21] A recent report estimated that scaled-up prevention could in theory prevent more than half of new infections over the next 10 years. See Stover J, Estimating the global impact of an AIDS vaccine. New York: IAVI, 2005. Widespread use of an AIDS vaccine could itself lower background prevalence, potentially quite substantially. This is one form of indirect benefit of immunization.

[22] Esparza J et al. Estimation of "needs" and "probable uptake" for HIV/AIDS preventive vaccines based on possible policies and likely acceptance (a WHO/UNAIDS/IAVI study). Vaccine 2003; 21(17-18): 2032-41. AIDS vaccines may eventually be used broadly even in low-prevalence countries if they prove safe and long-lasting and their price falls considerably. Assuming targeted rather than general population vaccination in low-prevalence countries reduces total vaccine benefits modestly, but lowers global demand for vaccine – and raises the cost-effectiveness of vaccination – quite dramatically.

including sex workers and their clients, injecting drug users, men who have sex with men, and soldiers. We assume that these programs will reach 50 percent of those at high risk during the initial period and 50 percent of new entrants to these populations every year thereafter.

Countries with generalized epidemics (for our purposes, those with adult prevalence above 2 percent) will attempt broad vaccination of adolescents and adults during an initial catch-up period. Since it is unclear how quickly developing countries will be able to reach large numbers of adults with an AIDS vaccine, and how rapidly suppliers will be able to scale up production, we consider two alternative projections of uptake. The more conservative projection, used in Scenarios 1 and 2, assumes that 25 percent of adults in high-prevalence countries are vaccinated over the first 10 years, while the higher projection underlying Scenarios 3 and 4 supposes catch-up vaccination of 50 percent of adults. After this initial period, we assume that mass vaccination will be replaced by routine immunization of adolescents in high-prevalence countries. At steady state, our model projects that coverage of new cohorts (15-year-olds) will be comparable to what each country currently achieves in routine childhood immunization.

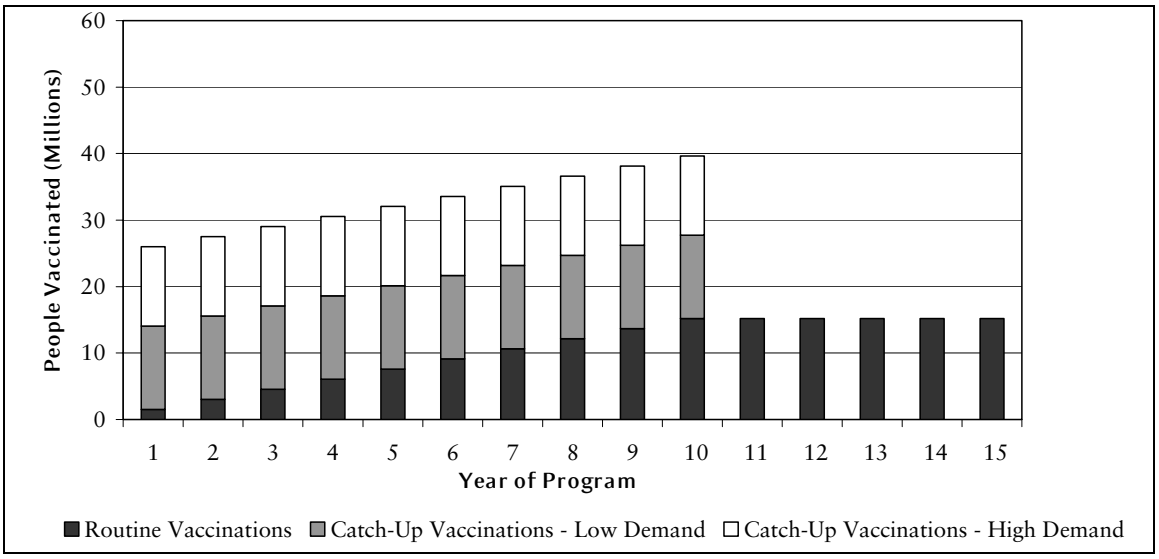
We further suppose that steady-state coverage is reached ten years after sales begin under the AMC. Individual countries may ramp up more quickly; this lag also incorporates differences in when country programs begin. Catch-up vaccination is spread evenly over these first 10 years.

Finally, we include in our analysis all countries that would be eligible according to the criteria proposed in Chapter 2: all countries with gross national income per capita below $1000 (in 2002) plus those with income between $1000 and $5000 and HIV prevalence above five percent.[23] The one exception to these criteria is China, which we do not include on the assumption that its income will almost certainly exceed the cut-off by the time a vaccine is available.

Under these assumptions, the more conservative demand scenario projects that 209 million people would be vaccinated in eligible countries during the first 10 years of the program, while the higher-demand scenario predicts 328 million vaccinations over this initial period. In each case 15 million people would be vaccinated every year thereafter. (The number of vaccine doses would of course be higher, at least three-fold greater for a vaccine requiring three doses.) Most of this vaccination (over 90 percent) is in high-burden countries (those with adult prevalence above 2 percent). Figure 7 shows the time-course of vaccination.

[23] This second category currently includes South Africa, Botswana, Swaziland, and Namibia.

Figure 7. Vaccine uptake



As Figure 7 illustrates, our assumptions imply an abrupt drop-off in vaccine demand at the end of the ten-year catch-up period. In practice, any decline after an initial peak would be more gradual, since catch-up vaccination would almost certainly continue as long as large numbers of at-risk adults remained unvaccinated and since different countries would follow different adoption and catch-up timetables. Moreover, revaccination would boost demand in later years. Thus our estimates of long-run demand should be considered conservative.

This simple picture of vaccine use and uptake unavoidably neglects many important factors. A comprehensive analysis of AIDS vaccine demand (for which the recent study commissioned by the Malaria Vaccine Initiative could serve as a model) would examine how vaccine purchase and use in the public and private sectors, as well as the rate of adoption, might depend on vaccine characteristics as well as price.

4.1.3 AMC terms, revenue to suppliers, and costs to donors and developing countries

As explained in Chapter 2, we propose that the AMC quantity maximum be set so that the commitment would be exhausted in about 10 years. Thus the maximum is 200 million in Scenarios 1 and 2, which use the conservative demand projection, but 300 million in Scenarios 3 and 4, which assume higher demand. The corresponding guaranteed prices are $24 and $15, chosen to ensure that the net present value of the AMC payments to suppliers would be about $3.3 billion, using an 8 percent real discount rate.

The total costs of vaccine purchase and delivery, discounted to the first year of the program at 4 percent, add up to $11.0 billion for Scenarios 1 and 2 and $12.4 billion for Scenarios 3 and 4. Of this total, AMC high-price payments constitute about 30-40 percent, while vaccine costs at the long-term low price add only another 10 percent. Delivery costs account for the remaining 50-60 percent of total discounted costs, and are thus critical to vaccine cost-effectiveness. It is difficult to project how much it will cost to deliver an AIDS vaccine, since developing countries have little experience vaccinating adolescents and adults on a large scale. We have assumed a cost of $5 per dose, or $15 total for a vaccine

requiring three doses. Although this is considerably more than the cost of adding a new vaccine to an existing vaccination schedule, it is less than the estimated total cost of childhood immunization in resource-poor settings.

4.1.4 Estimating cost-effectiveness

The model examines the benefits and cost-effectiveness of an AMC in two ways. First, it estimates the total benefits of an AIDS vaccine in eligible countries and the total costs to sponsors and recipient countries of purchasing and delivering the vaccine under the AMC. This approach, which we will call "total" cost-effectiveness, implicitly assumes that without an AMC there would be no vaccine. In a sense, the analysis asks: "If an AMC can bring us a vaccine, is it a good investment?"

The second approach considers instead the incremental benefits and costs of an AMC, on the assumption that it gives the developing world a vaccine sooner than one would otherwise become available. The benefits in this case are the additional lives saved or extended by having the vaccine sooner, while the costs are those of purchasing and delivering the vaccine under the AMC, minus what would have been spent without an AMC.[24] It is impossible to know, of course, by how much an AMC would hasten vaccine availability. For illustrative purposes, we assume here that an AMC would advance development and debut of a vaccine for the developing world by five years (by increasing industry investment in research and development) and speed adoption by an additional five years (by encouraging both investment in production capacity and planning for use; see Chapter 1). In Section 4.5.5 we explore the consequences of relaxing this assumption. While this second approach, which we will refer to as "incremental" cost-effectiveness, is probably the more appropriate way to evaluate AMC cost-effectiveness, the first approach provides an overview of vaccine benefits and costs and has the virtue of simplicity.

Neither approach directly considers the costs of developing or manufacturing a vaccine, whether borne by private firms or by governments and other sponsors. Thus our analysis does not address whether development of an AIDS vaccine is a good social investment but asks instead whether vaccine purchase and use under the terms of an AMC is cost-effective.

4.2 Benefits and cost-effectiveness under the four scenarios

We now present results of applying the model to the four scenarios outlined at the start of this chapter.

4.2.1 Scenario 1: Baseline vaccine

First, we consider the impact of a classical preventive vaccine with efficacy of 50 percent and 10 year duration, using the more conservative demand projection. Such a vaccine would meet the standards we propose in Section 2, but should be considered a minimal, first-generation product. The vaccine would be purchased under the terms of the proposed

[24] To calculate costs in the absence of an APC, we must make assumptions about prices. We suppose that an AIDS vaccine would initially cost $10 per course and that this price would decline over 15 years to $6. Assuming higher prices would increase the estimated cost-effectiveness of an AMC.

lower-demand AMC: $24 for each three-dose course for the first 200 million courses, $6 for each course thereafter.

Benefits

A vaccine with these characteristics used in the way we describe above would save 91 million DALYs over the first 10 years, corresponding to about 3.1 million infections averted.[25] In the absence of treatment, each infection averted means a life saved. Much of this impact (55 percent) would come from catch-up vaccination of adults in high-prevalence countries. After the program reaches steady-state, routine vaccination would save 6.4 million DALYs and avert about 210,000 infections every year.

These estimates underestimate the likely impact of such a vaccine in at least two ways. First, many high-prevalence countries would probably continue broad vaccination of adults after the initial catch-up period, with booster shots if possible, in order to overcome the relatively short duration of protection. Although it is difficult to know how successful such a strategy would be, maintaining the rates of immunity achieved in adolescents would almost double the impact of the vaccine at steady-state. Second, considering the indirect effects of vaccination would add substantially to the total benefits.

Cost-effectiveness

As explained above, we calculate cost-effectiveness in two ways. Dividing total costs of vaccine purchase and delivery under the terms of the AMC by total vaccine benefits gives an estimate of $67/DALY saved. This implies that even if the resulting vaccine is only modestly effective, an AIDS vaccine AMC is a highly cost-effective investment, scoring well below the conventional $100/DALY threshold. For comparison, Table 2 shows cost-effectiveness estimates for a variety of health interventions in developing countries.

It is probably too pessimistic to assume that no vaccine would be developed without an advance market commitment. Evaluating "incremental" cost-effectiveness yields a cost-effectiveness ratio of $96/DALY, higher than if all costs and benefits are considered, but still attractive compared to other health interventions. If the total advance is less, cost-effectiveness falls (see Section 4.5.5).

[25] This estimate adds up benefits resulting from vaccination occurring during the first 10 years. Because of the lag between HIV infection and AIDS, the benefits themselves (illness and deaths avoided) come several years later.

Table 2. Cost/DALY for different health interventions[26]

Intervention	Cost per DALY saved (US$)
Other Vaccines	
EPI cluster	14-20
Hepatitis B, low prevalence	42-59
Hib	21-55
Other communicable disease interventions	
TB prevention	635-1,082
Community-based DOTS for TB	53-79
Provision of ITBNs for malaria prevention	19-85
Malaria chemoprophylaxis	8-93
Other AIDS interventions	
Male condom distribution	1-99
Blood safety measures	4-43
STI diagnosis and treatment	45
VCT	68-82
PMTCT	34-819

4.2.2 Scenario 2: Baseline vaccine, high-demand

In this scenario, the same minimal vaccine is used more broadly, reaching 50 percent of adults in high-prevalence countries during the first ten years.

Benefits

In these circumstances the number of DALYs saved rises to 142 million over ten years, and 4.7 million infections are averted over this period. Benefits at steady state are the same as in Scenario 1.

Cost-effectiveness

Vaccine costs rise along with benefits as more people are vaccinated, but both total and incremental cost-effectiveness improve, to $60 and $72/DALY respectively. The additional vaccination is cost-effective because the recipients are young adults in high-prevalence countries and thus at relatively high risk.

4.2.3 Scenario 3: Superior vaccine

Next we consider a vaccine with considerably higher efficacy in preventing infection (80 percent) and longer duration (20 years), with vaccine uptake as in Scenario 1.

Benefits

This vaccine, adopted at this rate, saves almost 204 million DALYs over the first 10 years, which translates to approximately 6.8 million infections averted. At steady state, 17 million DALYs and 550,000 infections are averted every year. Raising efficacy from 50 percent to 80 percent accounts for about half of this increased impact, but doubling the duration of

[26] Adapted from: GAVI. Vaccines are cost-effective: a summary of recent research, Health, Immunization, and Economic Growth Research Briefing 2, Geneva: GAVI, 2004; Creese A, Floyd K, Alban A, et al. Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence. Lancet 2002; 359: 1635-42; Mills A and Shillcutt S, Copenhagen Consensus challenge paper on communicable diseases. April 2004; Hanson K et al, The economics of malaria control interventions. Geneva: Global Forum for Health Research, 2004.

protection has an equally dramatic effect, as the protection afforded to vaccinated adolescents now extends far further into adulthood (see Figure 8 below).

Cost-effectiveness
The costs of vaccine purchase and delivery are the same as in Scenario 1, but vaccine benefits are far higher. The ratio of total costs to benefits (total cost-effectiveness) falls to $28/DALY; if only the incremental costs and benefits of advancing vaccine availability by 10 years are considered (incremental cost-effectiveness), the ratio is $40/DALY.

4.2.4 Scenario 4: Superior vaccine, high demand

Finally, we estimate the benefits of the superior vaccine when it used more broadly.

Benefits
Now vaccination saves 308 million DALYs over 10 years and averts 10.3 million infections. Note that the combination of an improved (but still imperfect) vaccine and higher uptake increases total benefits by more than three-fold (compare to Scenario 1). At steady state, benefits are as in Scenario 3.

Cost-effectiveness
AMC cost-effectiveness now falls to $21 and $26/DALY by the two methods. Thus even without considering the potentially very large indirect benefits, AIDS vaccination in the context of an AMC can be more cost-effective than almost any other HIV/AIDS intervention, and comparable to vaccination against other diseases in the developing world.

4.3 Disease-modifying vaccines

Many of the AIDS vaccines now in the development pipeline are not expected to strongly protect against HIV infection. Instead, it is hoped that they will help the immune system control viral replication after infection and thus delay progression to clinical disease and death. Vaccines of this type could bring substantial benefits and cost savings by extending life and postponing the need for antiretroviral therapy. For example, a vaccine that extended the life after HIV infection by 10 years (approximately doubling average survival time in the absence of treatment), would bring roughly the same direct benefits, measured in DALYs, as a vaccine that prevented 42 percent of infections altogether. If disease were postponed indefinitely, protection of this kind is essentially equivalent to 100 percent prevention of infection, at least at the individual level (see below).

This approach, based on the DALY formula, rests on many contentious assumptions, but it demonstrates one way to compare vaccines with very different modes of action.[27] Although our model is not designed to consider vaccines of the disease-modifying type, by entering an "equivalent efficacy" calculated in this way, one can obtain some sense of population and global benefits.

[27] DALYs are calculated using a complex formula that assigns weights to different types of illness or disability, discounts future disability or death, and values differently disease experienced at different ages. All of these features have been controversial.

This class of vaccine is expected to bring a second important benefit: lower HIV transmission. If the vaccine helps the immune system to reduce viral replication and thus viral load, transmission from vaccinated people (who are subsequently infected) to others may be reduced. Some models suggest that this effect could be substantial.[28] Thus these vaccines could bring large indirect benefits analogous to the "herd immunity" that conventional preventive vaccines provide.

Although for simplicity of analysis, we have treated infection-preventing and disease-modifying vaccines as distinct, it is likely that most vaccines would bring a combination of benefits. Some differential equation models of vaccine impact define three distinct quantities: efficacy in preventing infection, efficacy in delaying disease progression, and efficacy in lowering transmission. These models find that all three vaccine characteristics can be important in determining the long-term effect of an AIDS vaccine.[29]

4.4 Preventive vaccines in the context of widespread access to antiretroviral therapy

Developing countries and donors are committed to bringing effective antiretroviral therapy (ART) to the millions of people in urgent need in the developing world. Although access to ART remains low, especially in Africa where need is greatest, coverage is growing rapidly, and there is reason to hope that many more people will have access to treatment by the time a vaccine is available. An AIDS vaccine will remain vitally important, however, because treatment is not a cure. Treatment already imposes an enormous burden on both donors and developing countries, costing billions of dollars a year and straining fragile health systems; without a vaccine this burden will grow inexorably.

Widespread treatment alters the benefits of a vaccine in two ways. First, the background burden of disease that a vaccine can in principle avert is lower, since severe illness and death are reduced or postponed. UNAIDS has recently modeled the impact of increasing treatment coverage from about 10 percent today to 80 percent by 2012. The UNAIDS scenarios suppose – perhaps too conservatively – that ART will extend life by five years on average. With 80 percent coverage (and a few simplifying assumptions), this would reduce the total DALY burden of AIDS by a modest 9 percent. Thus the direct health benefits of the vaccines described in our four Scenarios would be reduced by a corresponding amount. If treatment is more successful in postponing serious illness and death – as it has been in the developed world – both the burden of AIDS and the absolute impact of a given vaccine would of course fall further.

On the other hand, vaccination in an environment of widespread ART would bring a very important additional class of benefit in the form of reduced treatment costs. The UNAIDS scenario estimates that 18.3 million people will be on treatment in 2025 in developing countries, 14.9 million of those in countries eligible for vaccine purchase under our proposed AMC. If treatment costs $600 per person per year, this corresponds to an $8.9 billion annual burden of treatment costs in eligible countries. If one further supposes that

[28] Barth-Jones DC, Chegulet BK, Longini I, et al. Modeling the potential impact of a partially effective HIV vaccine in a generalized African HIV-1 epidemic: evaluating strategies for HIV vaccine use. Technical report 03-08. Emory University, Rollins School of Public Health, Department of Biostatistics, June 2003.
[29] Ibid.

vaccination would reduce the number of people on treatment by the same fraction as it reduces new infections, the first-generation vaccine of Scenarios 1 and 2 would save about $600 million in treatment costs every year. The better vaccine of Scenarios 3 and 4 would bring $1.9 billion in annual savings. Vaccines that delay disease could also reduce treatment costs, especially if they eliminate the need for treatment altogether in some people, or if they prevent many infections by reducing transmission. Our approach underestimates treatment cost savings for the same reason that it underestimates health impact, by leaving out indirect benefits.

Although neither the number of people on treatment decades from now nor its cost can be known with any certainty, this very simple analysis makes clear that the treatment costs averted by widespread vaccination could be very large. In fact, the savings from averted treatment costs could easily exceed the total costs of vaccine purchase and delivery. At steady state (and after the vaccine price has fallen to its long-term, lower level), these costs are only about $300 million annually. Costs are higher during the first years of the program, reaching a peak of about $1.1 billion in the high-demand scenarios, but treatment savings attributable to vaccination during this period would also be higher, since more people are being vaccinated.30 Thus the prospect of widespread access to treatment increases rather than reduces the value of an AIDS vaccine AMC to donors and developing countries. Access to treatment will always remain vitally important, however, since not all of those at risk will be vaccinated, and AIDS vaccines will probably not prevent all infections in vaccinated people.

4.5 Sensitivity analysis

Our estimates of vaccine benefits and cost-effectiveness depend, inevitably, on a number of assumptions and on the values of key parameters. In fact, one of the benefits of analyses of this type can be to shed light on the most important determinants of the overall value of a proposed investment. In this section we will consider briefly the consequences of varying both input parameters and our underlying assumptions on vaccine strategy.

4.5.1 Vaccine parameters

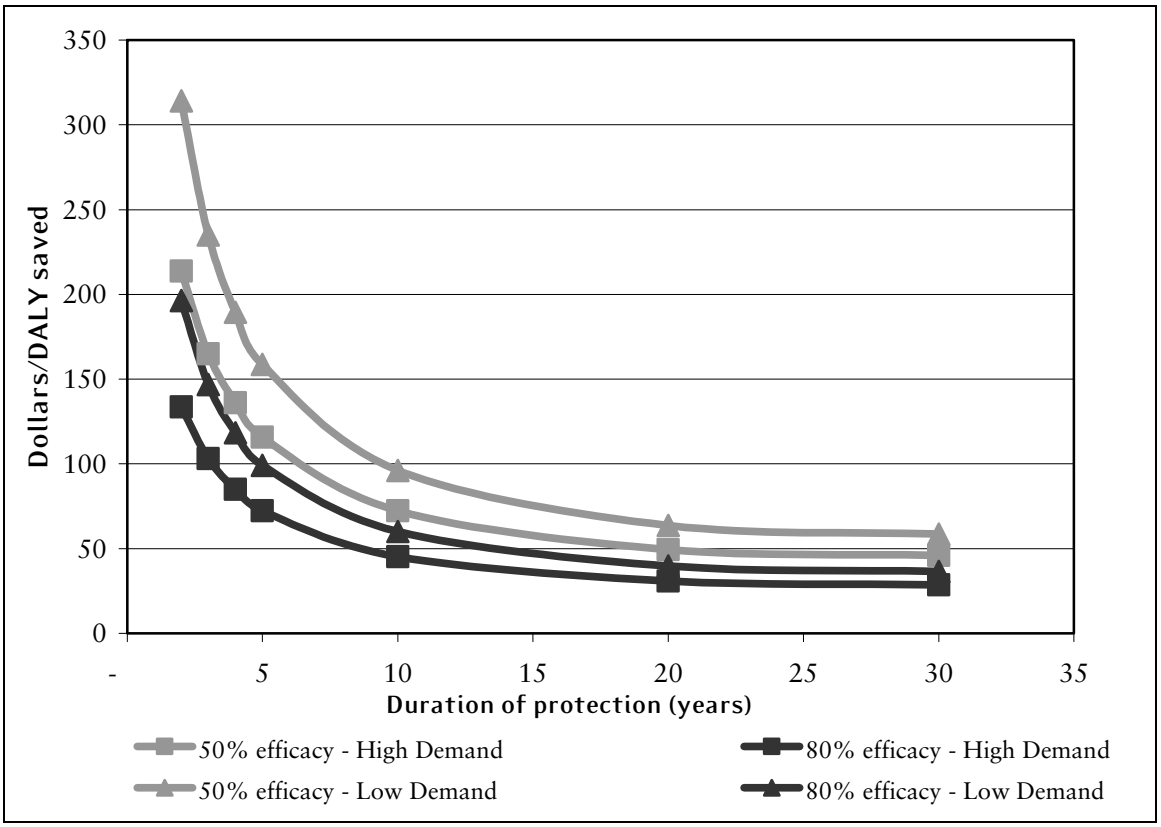
The efficacy of a vaccine is of course critical to its value. Indeed, the simple structure of the model we use here makes total benefits and cost-effectiveness directly proportional to efficacy: doubling efficacy doubles benefits and halves cost per DALY. The range of possible variation in efficacy is rather limited, however, since the AMC we have specified requires that it exceed 50 percent.

The impact of varying duration of protection is in some ways more striking. As Figure 8 shows, the cost-effectiveness of an AIDS vaccine AMC is poor if vaccines last less than five years; this finding informs our proposed minimum duration standard of five years. Cost/DALY decreases rapidly as duration increases past 10 years, and it continues to fall until duration exceeds 20 years. This dependence reflects the fact that HIV risk is spread over many years of adolescence and adulthood: a vaccine given to 15-year-olds must last decades to afford full protection. The drawbacks of short-duration vaccines might be

[30] As is the case with health benefits, treatment cost savings would not be realized until several years after vaccination.

substantially overcome by systematic revaccination or by greater reliance on mass vaccination of adults.

Figure 8. Dependence of vaccine advance cost-effectiveness on duration



4.5.2 AMC terms

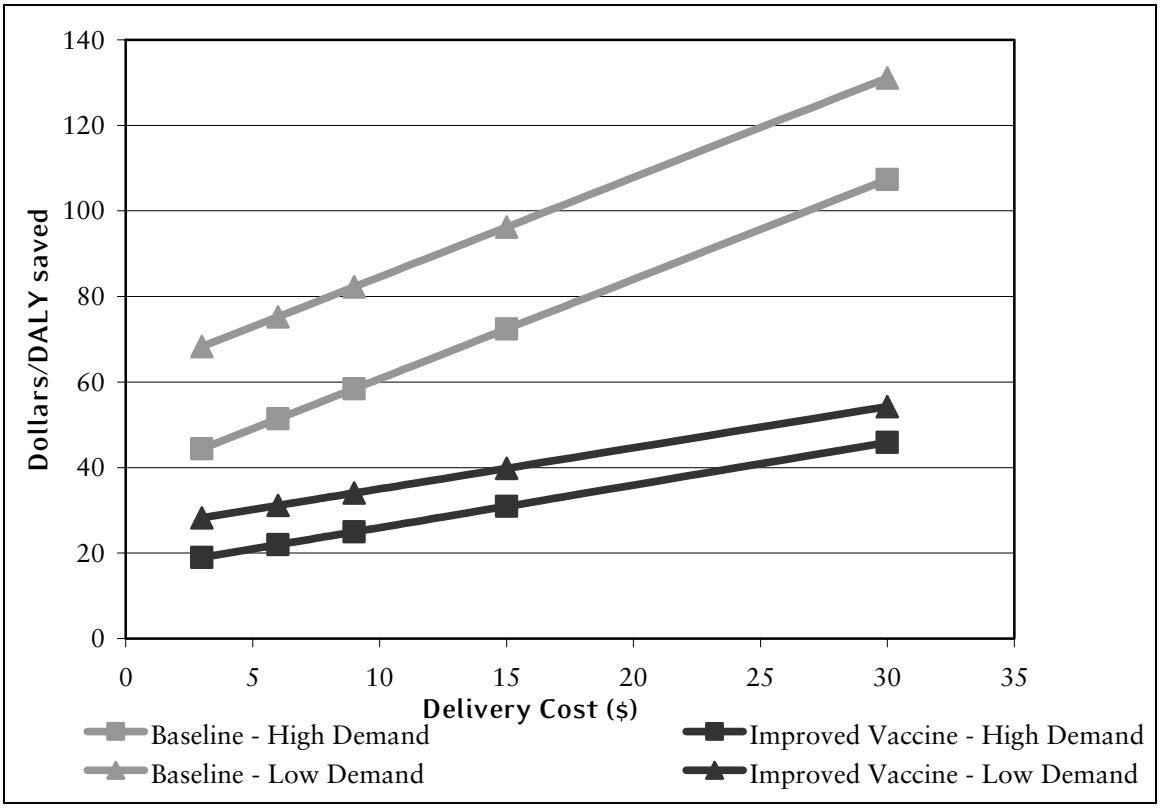
Since vaccine demand and use do not depend on price in our model, vaccine benefits do not depend on the terms of the AMC. Changing the AMC prices and quantities does alter cost-effectiveness, however. Raising the guaranteed initial price has a significant but relatively modest effect. Doubling the initial price (while keeping guaranteed quantity constant) increases total costs by about 36 percent in the high-demand scenarios and by 30 percent in the low-demand scenarios. The $100/DALY threshold in total vaccine cost-effectiveness is reached at about $48 with the baseline vaccine and low update (Scenario 1). With the improved vaccine, this price can rise as high as $200 before the $100 mark is reached.

In practice, then, cost-effectiveness imposes an upper limit on the guaranteed price with a baseline vaccine. With a better vaccine, this is less of a consideration, and the price that can be offered is more likely to be limited instead by the total size of the AMC that donors are willing to fund. Our results are less sensitive to the long-term price, since payments at the $6 price proposed here contribute only 10 percent to total costs. To some extent, this is a consequence of discounting, since these purchases begin only after the commitment is exhausted in the 10th year.

4.5.3 Delivery costs

AMC (and vaccine) cost-effectiveness is quite sensitive to delivery costs. Doubling the estimate of costs per course to $30 brings the total cost per DALY averted of the baseline vaccine with low uptake to $101, while incremental cost-effectiveness rises to $131 (see Figure 9). Thus the choice of vaccine delivery strategy will be critical not only to vaccine benefits (see below), but also to cost-effectiveness.

Figure 9. Dependence of vaccine advance cost-effectiveness on delivery costs



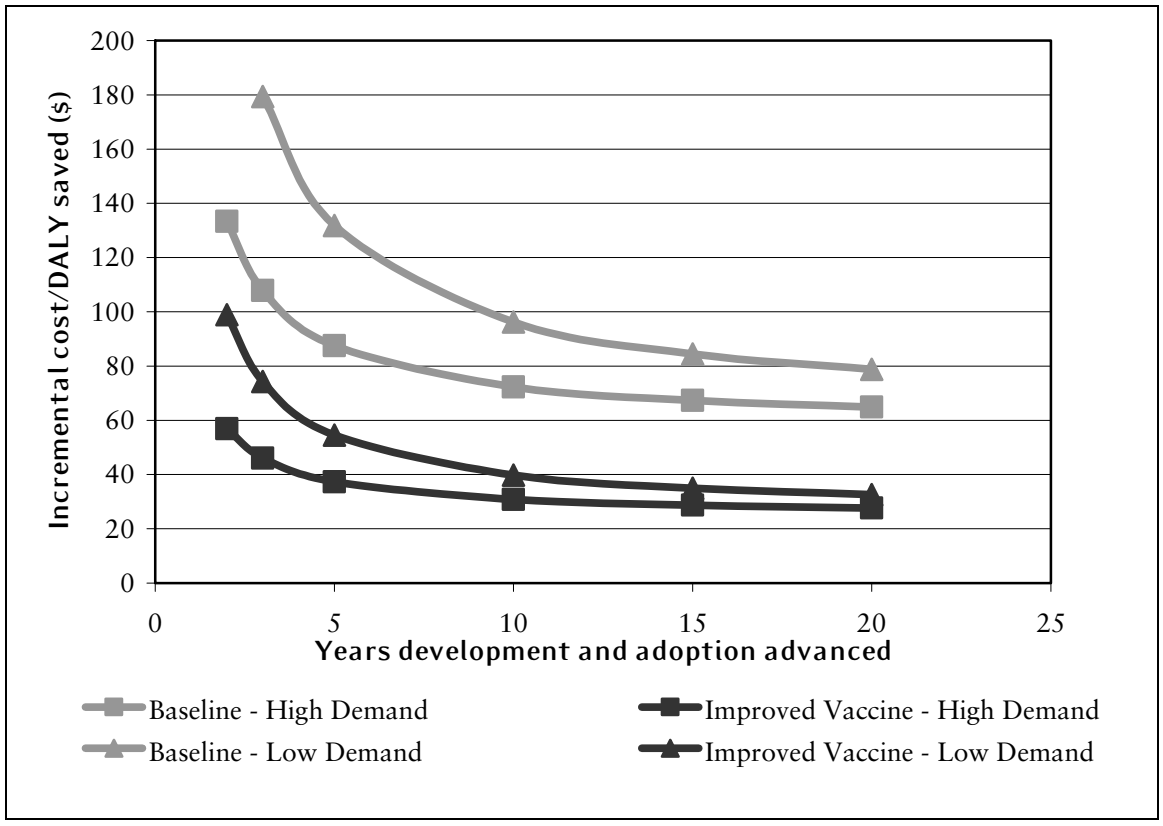
4.5.4 Background burden of disease

We have based our analysis on UNAIDS' projections of the epidemic for 2025 (and on demographic projections from the UN Population Division). Clearly the absolute benefits of an AIDS vaccine will be greater if more dire predictions (particularly for China and India) prove accurate. On the other hand, if prevention efforts bear fruit and more countries in East and Southern Africa see prevalence fall as it apparently has in Uganda, the number of infections to be averted by vaccination might be far lower than envisioned by UNAIDS. Although we have not attempted to explore the implications of alternative future scenarios for the epidemic, we have repeated our estimates using DALY burden and population estimates for 2000. The results are not dramatically different from those obtained using the projections for 2025, reflecting the essentially conservative character of the UNAIDS scenarios. Total benefits are higher with the 2025 numbers (as populations have grown), while long-term annual benefits are somewhat lower, largely as a result of the way the model handles population structure. Cost-effectiveness is marginally worse with the 2025 numbers.

4.5.5 Years that an AMC advances vaccine availability

We have calculated the cost-effectiveness of an AIDS vaccine AMC on the assumption that it would advance vaccine development and adoption by eligible countries by a total of 10 years. How great must this advance be for an AMC to be a good investment? Figure 10 shows that with our assumptions about prices in the absence of an AMC, bringing a baseline vaccine for the developing world forward five years is worth the additional expense by the $100/DALY standard, but only if it is broadly used, while an AMC that brings an better vaccine forward by only two years is a good value even if the lower-demand projection proves accurate.

Figure 10. Cost-effectiveness and years of advance by an AMC



These calculations assume that in the absence of an AMC an AIDS vaccine will initially cost $10 per course of vaccination, and that this price will decline linearly over 15 years to the long-term price of $6, which is assumed to be fairly close to the marginal cost of manufacturing. In reality, the initial price might be considerably higher, with a correspondingly lower demand. Since no reliable information is available to suggest what cost developing countries (and donors) would be willing to pay, and thus how demand might change with price, we have not attempted to model this more complex scenario.

4.5.6 Vaccination strategy

The costs and benefits of an AIDS vaccine will depend strongly on how it is used. Two features of our hypothesized vaccination strategy are worth reexamining. First, we have

assumed that countries with relatively low prevalence will focus vaccination campaigns largely on high-risk populations. If instead all eligible countries attempt mass vaccination of adults and adolescents, the total number of people vaccinated would be far greater (the 300 million course commitment of Scenarios 2 and 4 would be exhausted in four years rather than 10), but total benefits would increase by only 40 percent. The cost per DALY saved more than doubles.

Our analysis can be challenged on several grounds, however. In practice it may be quite difficult to reach members of high-risk populations, especially where stigma and official harassment have driven them underground. Although the experience of successful HIV prevention programs demonstrates that these vulnerable and marginalized populations can be reached, the delivery costs may be considerably higher than for adolescents or the general population. Finally, we based our assumptions on the size and relative risk of high-risk populations on very limited data.

Another critical assumption of our analysis is the absence of revaccination. As explained earlier, this accounts for the importance of vaccine duration. The structure of the model makes it difficult to incorporate revaccination in a sophisticated way. We can approximate the extreme case of 100 percent successful revaccination with the baseline vaccine (assumed to last 10 years) by extending the duration of vaccine protection to 20 years and adding a second round of delivery costs after 10 years. With discounting, this is equivalent to increasing total delivery costs by about 70 percent. Total benefits increase by 50-60 percent, but cost-effectiveness increases only marginally. If only a single booster shot is required to extend protection, costing $5 to deliver, the impact on cost-effectiveness is much more dramatic, about 25 percent. In reality, revaccination programs would be not be 100 percent effective, and their per-person costs might be higher than those of initial immunization.

4.6 Limitations and future work

The analysis presented here should be considered a rough first estimate of the benefits of an AIDS vaccine and of the cost-effectiveness of an advance commitment for its purchase. Although many aspects of the analysis could be refined, we believe the two most important priorities for future work are estimation of the indirect benefits of vaccination and comprehensive study of likely vaccine demand. IAVI has begun work in both areas.

Incorporating indirect effects would substantially increase the estimated benefits of AIDS vaccines. Preliminary results from an analysis by the Futures Group for IAVI suggest that the impact of an AIDS vaccine could be several times greater than we project here; although the two approaches are difficult to compare directly, most of the difference can probably be attributed to indirect benefits.[31]

[31] The Futures Group study, which drew on published mathematical models to ascertain a relationship between vaccine coverage and efficacy and long-term reduction in prevalence, estimated that a 60% effective vaccine could prevent 47 million new infections in the first 15 years of use. Much of this effect is indirect, reflecting lower infection rates for both vaccinated and unvaccinated people after several years of vaccination have altered the course of the epidemic. See Stover J, Estimating the global impact of an AIDS vaccine. New York: IAVI, 2005.

More sophisticated treatment of vaccine demand would affect the results in more complicated and less predictable ways, since demand would almost certainly depend on the nature of the vaccine as well as on price, expected donor support, and the state of the epidemic and efforts to combat it. While demand for a highly effective vaccine might be substantially higher than we project, demand for a minimal vaccine could be lower. Moreover, demand outside eligible countries, which would also vary with vaccine characteristics and price, would affect revenue to vaccine developers and should thus in turn influence the terms of an AMC.

Another important issue that we have not considered, primarily because there is so little available data, is breadth of protection. First-generation AIDS vaccines may well protect against only certain strains of the virus; this might very substantially limit their use as well as their benefits. Our analysis could apply to a single qualifying vaccine that protects against all strains or to a set of vaccines that together cover most of the important strains.

4.7 Summary of impact analysis

Our modeling demonstrates that widespread access to even a partially effective AIDS vaccine in the developing world would bring enormous benefits. Even under quite conservative assumptions about vaccine uptake, and even without considering the potentially very large indirect effects of vaccination, an AIDS vaccine would avert millions of infections and save tens or hundreds of millions of DALYs.

A better vaccine brings substantially greater benefits than one that just meets our proposed minimum standards. Efficacy matters, but so does duration of protection, since adolescents, one of the most likely target populations for an AIDS vaccine, remain at risk of HIV infection for decades. Although we do not model explicitly the impact of vaccines that postpone or prevent the development of serious disease rather than preventing initial infection, we argue that vaccines of this type could also bring large benefits.

AIDS vaccine purchase and use under an AMC of the kind we propose here would be a highly cost-effective investment. If all costs and benefits are considered, cost-effectiveness ranges from $67 to as little as $21 per DALY saved, depending on vaccine characteristics and on the scale of catch-up vaccination in the first years after a vaccine becomes available. Even if one considers only the incremental costs and benefits of advancing vaccine development and adoption by ten years with an AMC, cost-effectiveness remains below $100/DALY in most of the scenarios that we consider. With a better vaccine, an AMC would be a cost-effective investment by this standard even if it advanced availability by only two or three years. Thus an AIDS vaccine compares well with other vaccines and very well with other HIV/AIDS interventions.

An AIDS vaccine AMC could also bring very large savings by averting costs of antiretroviral treatment. According to recent UNAIDS projections, as many as 18 million people could be on treatment in the developing world by 2025 if ambitious access targets are met. Our very preliminary (and conservative) estimates suggest that an AIDS vaccine could save 0.6-1.9 billion dollars every year in treatment costs averted. These savings could easily exceed the total costs of AIDS vaccine purchase and delivery under the terms of an AMC.

5.0 Conclusions

The analysis presented in this report supports three main conclusions. First, it should be possible to design and implement an AMC for AIDS vaccines that would be technically feasible, credible to industry, and attractive to industry, sponsors, and developing countries. A number of technical challenges remain, especially in setting the size of a commitment and the guaranteed and long-term prices (see below), but these challenges seem manageable. Other aspects of an AMC, including technical specifications for the vaccine, legal arrangements, and the role and composition of the IAC, do not seem to pose substantial obstacles.

Second, consultations with industry suggest that there is considerable interest in and support for an AIDS vaccine AMC within the private sector, as well as a clear sense that there has been progress toward developing a commitment that would meet industry's needs. Prices, and the mechanisms for setting them, emerged as the most troublesome elements of the proposed commitment. Many firms felt that the proposed prices were too low in light of possible manufacturing costs, and some were uncomfortable in principle with setting prices before these costs can be known. There was no consensus on the impact of an AMC: some firms felt that a commitment with the outlined size and structure would have a substantial effect on private sector investment in AIDS vaccine R&D, while others argued that the commitment was too small or that progress was limited by scientific obstacles rather than the size of the market. In general, however, industry seemed open to working with potential sponsors and others to overcoming the remaining barriers to an AMC acceptable to both sides.

Third, an AIDS vaccine AMC would almost certainly be a highly cost-effective investment for sponsors. A vaccine would bring very large health benefits and avert hundreds of millions of dollars every year in antiretroviral treatment costs. In most plausible scenarios the cost of vaccine delivery and purchase under an AMC would be less than $100 per DALY saved. It is not possible to know with any precision how much vaccine development and adoption would be accelerated by an AMC, but our analysis suggests that an AMC could be a very cost-effective investment even if it brings a vaccine into widespread use only a few years sooner.

Our analysis also suggests several particularly important areas for further work.

1. On the technical side, more work needs to be done to develop a broadly acceptable approach to determining the overall size of AMCs, including one for AIDS vaccines. Such an approach must produce a result consistent with the goals of an AMC, but it must also provide a rationale that both industry and potential sponsors find compelling.

2. For AIDS vaccines in particular, more work and perhaps new ideas are necessary to develop ways to set the guaranteed and long-term prices in the face of great uncertainty over manufacturing costs. It may make sense to build in substantial flexibility over prices, but this must be done in such a way that the commitment remains credible and the risk to donors manageable.

3. Guaranteeing adequate supply remains a big challenge, especially in the first years after a vaccine becomes available, when mass catch-up campaigns will probably be launched in many high-prevalence countries. The AMC as currently structured may not provide sufficiently strong incentives for developers to bring in additional suppliers or to allocate limited supply to eligible countries in preference to other markets.

4. More work should be done to understand how an AMC might affect the behavior of different segments of industry at different stages of vaccine development, and how pull incentives of this kind can be designed to work well with push funding.

5. Finally, a much more comprehensive analysis of likely demand for AIDS vaccines is needed, to inform the terms of an AMC, to plan for manufacturing and delivery, and to provide greater certainty to industry and donors.

Annex 1. Annotated Term Sheets

Term Sheet for Advance Market Commitment

Framework Agreement

1.	**Parties:**	One or more nongovernmental, grant-making organizations (such as a foundation) or governmental grant-making organizations (such as the U.S. Agency for International Development or the U.K. Department for International Development) (each, a **"Funder"**)[1] and one or more pharmaceutical companies, biotech companies or emerging manufacturers[2] that will work within the Framework (as defined below) to develop eligible vaccine(s) (each, a **"Developer"**).

[1] The Framework and Guarantee Agreement term sheets are designed to accommodate a variety of Funders, despite the fact that there are substantial differences between governmental and nongovernmental organizations in areas such as funding capacity and ability to contractually commit to the Guarantee Agreement. Because traditional commercial mechanisms for ensuring compliance, such as letters of credit or escrow arrangements, would be unattractive to potential Funders as they would result in increased transaction costs and unnecessarily tie up funds that could be made available for more immediate opportunities, the Framework Agreement was structured as a bilateral contract. Once one or more Developers sign on to the Framework Agreement, the financial commitment of the Funders would become binding, and, in the event of a default by the Funders, the Developers would be able to pursue standard contract remedies, such as money damages and specific performance, to enforce their rights.

[2] The Framework and Guarantee term sheets do not discriminate among potential Developers and are designed to allow participation by pharmaceutical companies, biotechnology companies and emerging manufacturers.

2. Purpose: Create a legally binding series of agreements that guarantees the developer(s) of an HIV/AIDS vaccine that meets the requirements set forth in the agreements a specific price for each qualified sale of the vaccine in certain designated developing countries (the **"Framework"**).[3] The objective of this Framework is to reduce the rate of new HIV infections and the impact of AIDS in the developing world significantly, thus effectively ending or substantially blunting the global AIDS pandemic and improving the chances of developing countries to achieve their key economic and social goals as expressed by the Millennium Development Goals. The Framework is designed to achieve this objective by stimulating and accelerating the timeline for the development, licensure, and uptake of a preventive vaccine. Recent analysis suggests that in the absence of a vaccine, the number of new HIV infections among adults and children will increase from around 6 million a year today to 10 million annually by 2030. An AIDS vaccine of moderate efficacy and population coverage could cut the number of new infections by about a third, averting nearly 50 million infections avoided over a 15-year period. This Framework is designed to facilitate the purchase of a vaccine with approximately this level of epidemiological impact. A vaccine with higher efficacy and greater coverage would go even further to help roll back the pandemic.

3. Benefits to Funder: Fulfills the Funder's philanthropic mission (or a statutory or regulatory mandate, in the event Funder is a governmental organization) by giving Developers an economic incentive to (a) select and implement R&D projects that are likely to lead to the development of one or more HIV/AIDS vaccines that are effective against the clades prevalent in developing countries, and (b) establish manufacturing capacity for production of such vaccines.

[3] Each Framework Agreement will establish a specific price for qualified sales of an Approved Vaccine, by supplementing the "floor price" (*i.e.,* Minimum Co-Payment) paid by a vaccine purchaser (e.g., UNICEF) with a certain fixed payment to be made by the Funders. The Framework Agreement is not intended to displace, and indeed is specifically designed to work with, existing procurement systems. The Framework is sufficiently flexible that it can work within any procurement system, provided that the Minimum Co-Payment is tendered.

4.	**Benefits to Developers:**	Establishes a specific price (comprised of a Minimum Co-Payment (as defined below) by the purchaser and a guaranteed top-up payment by the Funders) for all eligible sales of the vaccine in developing countries that allows the Designated Supplier (as defined below) to cover, over the term of the agreements, R&D costs as well as manufacturing costs and to make an acceptable return on its investment. The guaranteed price will be based on a per-patient dosing regimen to provide the required prophylactic or disease-delaying benefit and will paid on all eligible sales up to the maximum number specified in the Guarantee and Supply Agreement. For example, if a course of three immunizations is required to provide the necessary immunity, the guaranteed price is $24 and the maximum number of treatments is 200 million, then the Developer would receive the guaranteed price of $24 only upon an eligible sale of all three doses comprising the course of treatment. If the Developer's total eligible sales equal the maximum number of treatments, 200 or 600 million doses, then the Developer would be entitled to a guaranteed payment of $4.8 billion.[4]
5.	**Principal Responsibilities of the Funder:**	Funder will (a) upon satisfaction of the conditions precedent set forth in Section 7, enter into a Guarantee and Supply Agreement (in the form attached to the Framework Agreement) with one or more Designated Supplier(s) (as defined below),[5] (b) fund the operation of the Independent Assessment Committee (as defined below) in accordance with budgeted amounts, (c) indemnify the members of the Committee for claims and losses arising out of the performance of their duties under the Framework Agreement and the Guarantee and Supply Agreement,[6] (d) retain the Contract Administrators (as defined below) to administer the Framework in accordance with budgeted amounts, (e) maintain in strict confidence any confidential business information submitted to it by the Developers, and (f) agree to be bound by decisions of the Committee acting within the scope of its authority.

[4] The price guarantee should be "per course of treatment" rather than "per dose." This approach provides incentives to ensure that all doses of multiple dose vaccines are administered, and encourages the development of vaccines requiring fewer doses where scientifically possible.

[5] Until a vaccine is approved under the conditions set forth in Section 7 of the Framework Agreement term sheet, the Funders are only required to commit to the Framework Agreement, and fund the functions of the Independent Assessment Committee. Once an Approved Vaccine is identified, the Developer has the right, and the Funder the obligation, to enter into the Guarantee Agreement with respect to that product. In other words, the Funder will not be required to pay for a vaccine unless and until a qualifying product is approved and the Developer agrees to make that product available to all Eligible Countries at a sustainable price after the price guarantee has been exhausted.

6.	**Principal Responsibilities of Developers:**	Each Developer will (a) provide confidential reports to the Independent Assessment Committee on the progress of its development efforts at the times specified by the Committee (it is contemplated that these reports would be high-level annual status reports at the outset and would increase in frequency and detail as the development efforts advance),[7] (b) provide such technical information as may be reasonably requested by the Committee in order to confirm that the conditions precedent set forth in Section 7 have been satisfied, and (c) agree to be bound by decisions of the Committee acting within the scope of its authority.
7.	**Conditions Precedent to Obligations of Funder:**	It will be a condition precedent to Funder's obligation to enter into and perform its obligations under the Guarantee and Supply Agreement that (a) the vaccine meet the technical specifications and usability requirements outlined in Section 8 below and (b) the Developer of such vaccine agree to continue to supply such vaccine after the Maximum Guaranteed Amount (as defined in Section 7 of the Guarantee and Supply Agreement) has been exhausted.[8]
8.	**Technical Specifications and Usability Requirements:**	For a vaccine to meet the technical specifications it must, subject to Section 10, satisfy the approval, safety and efficacy requirements set forth in Schedule A. For a vaccine to meet the usability requirements it must, subject to Section 10, satisfy the dosage, means of delivery, storage, shelf life and other requirements set forth in Schedule A.

[6] Indemnification is deemed to be particularly important to attract qualified members to serve on the Independent Assessment Committee.

[7] Developers may provide confidential information to the Independent Assessment Committee in two circumstances. First, Developers would submit progress reports to the Independent Assessment Committee during the term of the Framework Agreement. These reports will provide a way to evaluate the effectiveness of the mechanism during the research and early-development periods. These reports, if not promising, may permit the Funder to withdraw from the Framework Agreement under Section 22 of the term sheet. Second, for those Developers seeking to participate at a later date, the Framework Agreement requires some evidence that the Developer has a technology or expertise with scientific promise for the development of an Approved Vaccine.

[8] Although the Framework Agreement is designed to create an enforceable bilateral contract between the Developers and the Funders, the Funders would not be obligated to enter into the Guarantee Agreement until a product is tendered that meets certain minimum technical specifications, such as approval of both the product and its manufacturing process by a qualified regulatory body and certain safety, efficacy and use requirements.

9. Ongoing Supply Price Ceiling:

Each Developer of an Approved Vaccine (as defined in Section 12 below) that elects to enter into the Guarantee and Supply Agreement must agree to continue to supply such Approved Vaccine in Eligible Countries (as defined in Section 6 of the Guarantee and Supply Agreement Term Sheet) after the Maximum Guaranteed Amount has been exhausted at a price not to exceed the supply price ceiling set forth in Schedule A, as such ceiling may be amended by the Committee or the Developer as provided herein (the **"Ongoing Supply Price Ceiling"**).

The Base Price (as defined in Section 3 of the Guarantee and Supply Agreement Term Sheet) at which an Eligible Country must purchase a Qualifying Vaccine in order to qualify for the price guarantee before the Maximum Guaranteed Amount has been exhausted shall equal the greater of (a) US$1.00 (the **"Base Price Minimum"**) and (b) the Ongoing Supply Price Ceiling. Prior to entering into the Guarantee and Supply Agreement and from time to time during the term thereof, a Developer of an Approved Vaccine may agree to lower (but may not increase) the Ongoing Supply Price Ceiling.[9] Once a Developer lowers the Ongoing Supply Price Ceiling, it may not then increase it without the approval of the Committee.

10. Waiver of Conditions Precedent:

After the effective date of the Framework Agreement the Independent Assessment Committee may (by a 2/3 vote of its members or at the direction of the Funder) (a) waive or modify the technical specifications or usability requirements in a way that does not materially increase the cost of performance for a Developer, (b) increase the Ongoing Supply Price Ceiling, provided that the Developer can reasonably demonstrate that its Manufacturing Costs (as defined in Schedule A) cannot reasonably be reduced below ninety percent (90%) of the Ongoing Supply Price Ceiling, or (c) decrease the Base Price Minimum, provided that, in each case ((a), (b) and (c)), the Committee determines that waiver, modification or increase would preserve the goals and

[9] The Ongoing Supply Price Ceiling is designed to ensure that an Approved Vaccine will continue to be available at an affordable price once the Maximum Guaranteed Amount has been exhausted. However, because we cannot know today the actual cost of manufacturing an Approved Vaccine, the Framework establishes a mechanism that is designed to incentivize Developers to invest in cost-effective vaccine manufacturing technology and to protect Funders from paying for expensive vaccines. The Framework links the Ongoing Supply Price Ceiling to the Base Price, which is the minimum co-payment that is necessary to trigger the Funders' obligations under the price guarantee. If the Base Price for an Approved Vaccine is high, Eligible Countries (and donors) will be less likely to purchase that Approved Vaccine, which means that the Funders' price guarantee will not be triggered. The Developer is, therefore, able to effectively lower the Base Price, and thereby increase market demand, by agreeing to supply the product at a lower price once the Maximum Guaranteed Amount has been exhausted. Thus, the Framework mirrors the conditions in markets in the developed world by allowing Developers to compete based on price.

objectives of the Funders set forth in Section 2 above.

For purposes of illustrating the foregoing, if a specification called for 60% effectiveness, the Committee could, by a 2/3 vote of its members, reduce the requirement to 50% effectiveness, but could not increase it to 70% effectiveness under this provision.[10]

To the extent a waiver is granted for a Developer or an Approved Vaccine that is of general application, and is not specific to a particular proposed vaccine or Approved Vaccine, such waiver will be for the benefit of all Developers. For example, if the Committee determines that it would accept a specific decrease in efficacy in exchange for a specific increase in duration or expansion of the scope of the clades covered, it would be a general application waiver. If, however, a waiver is a result of a unique characteristic (or bundle of characteristics) of a proposed vaccine or an Approved Vaccine, it will not likely be a general application waiver. Nevertheless, the Committee will, wherever possible, structure waivers so that they are of general application and are not specific to a particular Developer or Approved Vaccine. Without disclosing specific confidential information of a Developer, the Committee will notify all Developers that have signed on to the Framework Agreement as to the terms of any general application waivers.

[10] Because the Developer should be assured that the Funders cannot change the rules of the game after the Framework Agreement is entered into, technical requirements cannot be changed to increase the burden of those requirements unless there is a significant change in circumstances with respect to the disease that would significantly reduce the need for a vaccine or undermine the specifications, such as a dramatic decrease in disease prevalence, a significant change in disease transmission or progression or a major advancement in treatment. As noted below, these types of changes would be subject to judicial review. Technical requirements may be decreased, however, at the discretion of the Independent Assessment Committee or the request of the Funders.

11. Testing and Acceptance: The Developer will submit the vaccine to the Independent Assessment Committee for testing and acceptance. The Committee will be responsible for making determinations with respect to whether a vaccine tendered by a Developer satisfies the conditions precedent set forth in Section 7, provided that the Committee will have the right to delegate this responsibility to one or more third-parties that it determines: are qualified to make such determinations and are independent and unbiased, such as, for example, the World Health Organization's prequalification process.[11] Further, the Committee will have the right to retain one or more consultants or rely on the actions of governmental or other third parties, such as the United States Food and Drug Administration or the European Medicines Agency, in making its determinations. In addition, the Committee will have authority to grant waivers of, or make modifications to, the application of specific technical specifications or usability requirements as provided in Sections 10 and 22.

12. Designated Supplier: If the Independent Assessment Committee determines that the conditions precedent have been satisfied (or if the conditions that have not been satisfied are waived or modified), then (a) the vaccine submitted by the Developer to the Committee will be deemed an **"Approved Vaccine,"** (b) the Developer of the Approved Vaccine will be deemed a **"Designated Supplier,"** and (c) at the election of the Designated Supplier, the Funder and the Designated Supplier will enter into the Guarantee and Supply Agreement within thirty (30) days of the date of the final, written determination of the Committee.[12]

[11] Because it would be extremely costly to create an Independent Assessment Committee *de novo* that is fully capable of independently evaluating, approving and monitoring the Approved Vaccines and their ongoing production, the Framework Agreement permits the Committee to rely on third parties and their procedures, such at the World Health Organization and its prequalification process.

[12] As noted above, the Framework Agreement is designed to be self-executing with respect to the Funders, providing the Developers with the right to enter into the Guarantee Agreement on the terms specified in the Framework Agreement. The Framework Agreement is also designed to permit more than one Developer to receive funds under the Guarantee Agreement. The Framework Agreement distinguishes between those Developers who are second because they are simply copying the First Developer's vaccine and those who are second because their independent research program happened to take longer.

13. Appointment and Composition of Independent Assessment Committee:

The Contract Administrator, in accordance with procedures and guidelines to be set forth in the Framework Agreement, will from time to time convene one or more committees (each, an "**Independent Assessment Committee**" or a "**Committee**"), which will be comprised of individuals with expertise in the following fields: (a) immunization practices, (b) public health, (c) vaccinology and vaccine development, manufacturing and commercialization, (d) pediatric and internal medicine, (e) social and community attitudes on immunization, (f) economics, (g) contract law and (h) the vaccine industry, in each case, as applicable, with developing country perspectives. The Framework Agreement will include procedures for the nomination and selection of members of each Committee (including the right of veto by representatives of the Donors, Developers and Eligible Countries) and rules for the ongoing participation of members, in each case that are designed to ensure that each Committee is independent, unbiased and conflict-free and retains the confidence of all of the constituent communities. Alternatively, the Framework Agreement could designate an existing institution, such as GAVI (provided that its mandate was expanded), to serve as the Independent Assessment Committee.

14. Actions of the Committee:

Each member of the Independent Assessment Committee will have one vote. Fifty percent of the members of the Committee, rounded up, will constitute a quorum. Except as provided in Sections 10, 20 and 22, all decisions of the Committee will be made by majority vote of the members at a meeting at which a quorum exists. If a specific institution is designated to serve as the Independent Assessment Committee, such as GAVI, then the Framework Agreement will provide that key decisions will require approval of the Board or Directors, or equivalent governing body. Procedures would need to be tailored to address the possibility of conflicts of interest and to provide for super-majority voting when required under the Framework.

15. Duties of the Committee:

The Committee will (a) seek to identify independent, unbiased and expert-qualified institutions and procedures to assist with determining whether a product meets the technical specifications and usability requirements and that can provide ongoing review of product safety and efficacy and manufacturing, (b) if necessary, designate Approved Regulatory Countries and Approved Manufacturing Countries (as defined in Schedule A) from time to time, (c) evaluate products presented by Developers to determine if they satisfy the conditions precedent, (d) at its discretion or at the direction of Funder, (i) waive or modify the application of specific technical specifications or usability requirements pursuant to Section 10, (ii) increase the Ongoing Supply Price Ceiling, or (iii) decrease the Base Price Minimum, (e) if requested or as necessary, conduct multiple bilateral or multilateral meetings with

Developer(s) in order to provide information about testing and acceptance procedures, waivers and modifications to the conditions precedent, market demand and supply forecasting, disease epidemiology and other relevant information,[13] (f) designate Approved Vaccine(s) and Designated Supplier(s), (g) after an Approved Vaccine has been designated, monitor the sales and use of such Approved Vaccine for ongoing compliance with the technical specifications and usability requirements set forth in Section 8 and decertify any vaccine that is not in material compliance with such specifications and requirements, and (h) determine whether the technical specifications and usability requirements set forth in Section 8 or the Maximum Quantity or Funder's other payment obligations under the Guarantee and Supply Agreement should be modified in whole or in part based on *force majeure* criteria pursuant to Section 22.

16. Duties of Committee Members: Each member of the Independent Assessment Committee will, in the exercise of its authority under the Framework Agreement, have the same fiduciary duties (including duty of care and duty of loyalty) as the director of a Delaware corporation.[14]

[13] It is contemplated that the Developers would have the right to consult with the Independent Assessment Committee, much the same way that companies consult with the FDA in the United States, to discuss the design of clinical trials, the structure of drug approval applications, the country or countries in which such drug approval will be sought, the possibility of granting waivers and other issues relating to the approval of an Approved Vaccine.

[14] The duties of a corporate director under Delaware Law are the duty of loyalty, the duty of care and the duty of good faith. The duty of loyalty requires the director to place the corporation's interests above his or her own. The duty of care requires the director to act with certain minimum level of skill and deliberation. The duty of good faith requires that a director not act with bad faith, or engage in intentional misconduct.

17. Contract Administrator:

The Framework Agreement will provide for one or more institutions, such as the Vaccine Fund or the World Bank (each, a **"Contract Administrator"**), to monitor and implement the Framework and to facilitate the performance of the Funders under the Guarantee and Supply Agreement, including, for example, to serve as a secretariat to govern the administration of the Framework, to convene from time to time the Independent Assessment Committee, to implement decisions of the Independent Assessment Committee, and to administer the Guarantee and Supply Agreement (including collecting and disbursing the donor financial commitments as provided therein), to report on the progress of the Framework to the Funders and to perform such other administrative, support and other tasks as may be set forth in the Framework Agreement or Guarantee and Supply Agreement or otherwise requested by the Committee or the Funder, subject to the approved budget for administrative expenses. The initial Contract Administrator(s) will be designated in the Framework Agreement. The Framework Agreement will include procedures for the designation of additional or substitute Contract Administrator(s).

18. Budget:

The Framework Agreement will include a budgeting process to ensure that the reasonable expenses of the Independent Assessment Committee and the Contract Administrators will be reimbursed by Funder.[15]

19. Addition of New Developers to the Framework:

During the period beginning on the effective date of the Framework Agreement and ending thirty-six (36) months thereafter, one or more entities may become parties to the Framework Agreement (*i.e.*, Developers) upon written acceptance of the terms of the Framework Agreement by such entity. Thereafter, additional entities may become parties to the Framework Agreement upon (a) written approval by the Committee if the new entity has technology or expertise that shows promise for the development of an Approved Vaccine, and (b) written acceptance of the terms of the Framework Agreement by the new entity; provided that no entity may become a party to the Framework Agreement with respect to a product after it commenced clinical trials for such product without the consent of the Funder.[16]

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[15] A Funder's obligation to reimburse the Independent Assessment Committee is subject to the requirement that its expenses be reasonable. A Funder may want to give further consideration to mechanisms that would permit it to regulate the cost of the Committee without compromising the Committee's independence.

[16] These procedures were intended to strike a balance between, on the one hand, permitting companies with promising technology or relevant expertise to participate in the Framework and, on the other hand, discouraging free riders who would operate outside the Framework and sign on

20.	**Addition of New Designated Suppliers:**	The Independent Assessment Committee may determine that a newly-developed vaccine satisfies the conditions precedent in Section 7, subject to (a) its waiver and modification authority, and (b) any existing general waivers, provided that no "generic" product will be eligible (*i.e.*, a product that (i) is the "same" as an existing Approved Vaccine (which determination will be made in accordance with the standards developed for determining sameness under the Orphan Drug Act in the U.S.) and (ii) substantially relies on data generated with respect to, or the regulatory approval for, an existing Approved Vaccine). Upon such a determination by the Committee, the Developer of the newly developed vaccine will have the right to become a party to the Guarantee and Supply Agreement, whereupon the Developer of the new vaccine will be deemed a "Designated Supplier" and the new vaccine will be deemed an "Approved Vaccine." The addition of new Designated Suppliers and Approved Vaccines will, in each case, be subject to the original Maximum Guaranteed Amount set forth in the Guarantee and Supply Agreement. For clarity, the Framework Agreement is not intended to displace existing patent and regulatory exclusivity regimes.
21.	**Reserved Rights of Developer:**	Developer reserves all rights, and the Framework will not apply, to sales of any Approved Vaccine (a) outside the eligible countries identified in the Guarantee and Supply Agreement, and (b) in the military or travelers markets.

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only at the last minute. If companies do not sign on the Framework, the agreement would lose its binding effect. Moreover, it would be difficult for the Funders to monitor the success of the Framework, particularly with respect to research and early development, without the periodic reporting by the Developers required under the Framework Agreement. Funders may wish to strike a different balance, such as allowing companies to join the Framework up until they commence pivotal trials.

22. Force Majeure

In the event that there is (a) a substantial change in circumstances with respect to the HIV/AIDS in the countries identified in the Guarantee and Supply Agreement, including its incidence, its characteristics or methods for its treatment or prevention, such that the technical specifications or usability requirements outlined in Section 8, or the Base Price Minimum or Ongoing Supply Price Ceiling set forth in Section 9, no longer achieve the original objectives, or (b) a substantial change in manufacturing technology for vaccines such that the Ongoing Supply Price Ceiling outlined in Section 9 is reasonably expected to exceed the [average] Manufacturing Cost of "Approved Vaccines" by more than [thirty percent (30%)], the Committee, if requested by the Funder, will have the right (by a 3/4 vote of its members)[, using the criteria set forth in Schedule C,] to (a) modify the technical specifications or the usability requirements, as applicable, even if such modification increases the cost of performance by a Developer, (b) reduce the Maximum Guaranteed Amount or the Funder's other financial obligations to reflect changes in the number of eligible countries or the incidence of untreated HIV/AIDS in those countries, (c) decrease the Ongoing Supply Price, (d) increase the Base Price Minimum, or (e) terminate the Framework Agreement[; provided that no such change shall have any affect on the rights and obligations of a Designated Supplier of an Approved Vaccine with respect to a Guarantee and Supply Agreement with respect to such Approved Vaccine that has been executed by such Designated Supplier prior to any such decision by the Committee]. Unlike other decisions of the Committee, these decisions will be subject to judicial review by an appropriate forum to determine whether the Committee abused its discretion.[17]

[17] The Framework Agreement for an early-stage vaccine could be in force for a decade or more before a vaccine candidate is presented for final review to the Independent Assessment Committee. Accordingly, a force majeure provision permitting the Committee, at the request of the Funders, to alter the Framework Agreement based upon extraordinary events has been included. The force majeure clause would void or alter the Framework Agreement in the event of major changes to technology, disease epidemiology, etc. that make a vaccine either inappropriate or unnecessary or that would require a change in the specifications that would be more burdensome to the Developers. These determinations require the approval of a super-majority of the Committee and are subject to judicial review.

23. Representation and Warranties: The Framework Agreement will include standard representations and warranties of the parties, including representations and warranties by the Funders: (a) that they have authority to enter into the Framework Agreement and the Guarantee and Supply Agreement, (b) that, once executed, such agreements will be binding and enforceable in accordance with their terms, and (c) with respect to each governmental entity that is a Funder, that any sovereign immunity has been waived, and that all necessary appropriations or other approvals have been obtained to authorize, and that no further appropriations, approvals or authorizations are required with respect to, the financial commitments of that Funder.

24. Indemnification and Insurance: The Funder [and the Developers each] will indemnify the members of the Committee, or if an institution is designated, such institution, as well as the Contract Administrator(s), for claims and losses arising out of the performance of their duties under the Framework Agreement and the Guarantee and Supply Agreement.[18] In addition, the Funder will maintain director and officers insurance or equivalent policies for the benefit of the members of the Committee, any such institution and the Contract Administrator(s).

25. Term and Termination: The term will begin on the date that [__] Developers have executed the Framework Agreement (the **"Effective Date"**) and, unless earlier terminated pursuant to Section 22 or this Section 25, continue until the [_____] anniversary of that date, unless a Guarantee and Supply Agreement has been entered into prior to such anniversary in which case the term will continue until the later of such anniversary and the expiration or earlier termination of the Guarantee and Supply Agreement.

Funder will have the right to terminate the Framework Agreement (a) after the [_____] anniversary of the Effective Date if no Developer has commenced GLP toxicology studies for a product that shows reasonable promise to become an Approved Vaccine, (b) after the [_____] anniversary of the Effective Date if no Developer has commenced clinical trials for a product that shows reasonable promise to become an Approved Vaccine, (c) after the [_____] anniversary of the Effective Date if no Developer has commenced a pivotal clinical trial designed to demonstrate that a product meets the technical specifications and the usability requirements for an Approved Vaccine, (d) after the [_____]

[18] It is contemplated that this indemnification will be similar to that which is provided to officers and directors of corporations. Accordingly, the indemnification of the Independent Assessment Committee may exclude intentional misconduct or actions that are conducted in bad faith or for personal gain.

		anniversary of the Effective Date if no Developer has filed an NDA or other comparable filing for a product that meets the technical specifications and the usability requirements for an Approved Vaccine, and (e) after the [_____] anniversary of the Effective Date if no Developer has entered into a Guarantee and Supply Agreement with respect to an Approved Vaccine.[19]
26.	**Remedies in the Event of Breach:**	The Developers will have the right to pursue all available contract remedies, including damages, specific performance and other equitable relief.[20]
27.	**Dispute Resolution:**	[Arbitration under AAA rules in NY, NY.]
28.	**Governing Law:**	[New York law.]
29.	**Waiver of Immunity:**	If the Funder is a sovereign, it will (a) acknowledge that the transactions are subject to private commercial law, and (b) waive sovereign immunity.
30.	**Other Provisions:**	Other covenants, terms and provisions as requested by legal counsel to Funder or the Developers.
31.	**Exhibits:**	Guarantee and Supply Agreement.

[19] The Funders have the right to terminate the Framework Agreement if certain interim milestones have not been achieved in a timely manner. This provision is included to provide the Funders with an early out if the Framework does not appear to be stimulating productive research and development activities. This would permit Funders to pursue other, more-promising opportunities.

[20] Funders may wish to consider liquidated damages provisions to bolster the credibility of their commitment.

Schedule A to Term Sheet for Framework Agreement (HIV/AIDS)

I Technical Requirements

A. Indication:

1. To prevent HIV infection or onset of clinical disease due to HIV

B. Target Population:

1. HIV-negative adults and adolescents in regions where viral subtype A or C predominates

C. Efficacy Requirements

1. 50% efficacy in preventing infections or a doubling of average time between infection and disease [based on evidence TBD]

D. Duration of Protection

1. At least five years [provision for contingent payments if duration not known at time of licensure]

E. Interference

1. No interference with other vaccines

F. Regulatory Approval and Quality Control

1. Regulatory approval of a product[, with labeling that meets or exceeds the other technical specifications and usability requirements set forth herein,] in one or more of Canada, France, Germany, Italy, Japan, [Mexico], Spain, the United Kingdom, the United States, [others] and such other countries with regulatory standards and procedures that are at least equivalent to those in the foregoing countries, as the Independent Assessment Committee may designate from time to time (each, an **"Approved Regulatory Country"**). The Committee will have the right to remove any Approved Regulatory Country if its regulatory standards and procedures change after the effective date of the Framework Agreement or the date that it was approved by the Committee, as applicable.

2. Manufacture of product in one or more of Canada, France, Germany, Italy, Japan, [Mexico], Spain, the United Kingdom, the United States, [others] and such other WHO-qualified countries with regulatory standards and procedures that are at least equivalent to those in the foregoing countries, as the Independent Assessment Committee may designate from time to time (each, an **"Approved Manufacturing Country"**). The Committee will have the right to remove any Approved Manufacturing Country if its regulatory standards and procedures change after the effective date of the Framework Agreement or the date that it was approved by the Committee, as applicable.

3. In lieu of one or both of the foregoing requirements, the Committee may rely on an independent, unbiased, expert third party (*e.g.*, the WHO) to determine that the product meets or exceeds the other technical specifications and usability requirements set forth herein, and to ensure that the facilities where, and conditions under which, the product is manufactured are in compliance with Good

Manufacturing Practices and other applicable international standards with respect to the manufacture, holding and shipment of vaccines, in each case throughout the term of the Guarantee and Supply Agreement.

II Usability Requirements

A. Dosage:

1. Three doses or fewer

B. Route of immunization:

1. Any, provided conducive to use on a large scale in Eligible Countries as defined in the Guarantee and Supply Agreement

C. Presentation:

1. Multi-dose vials

D. Storage

1. **to be determined**
2. Two-year shelf life

E. Safety Requirements

to be specified, consistent with existing practices by UNICEF and PAHO

III Ongoing Supply Price Ceiling

1. The Ongoing Supply Price Ceiling will be [TBD], which amount will be adjusted on an annual basis to account for any changes in [the Producer Price Index for Chemicals and Allied Industries in the United States, or other similar index with respect to the country where the product is manufactured,] from the effective date of the Framework Agreement.
2. The Ongoing Supply Price Ceiling may be adjusted upwards or downwards based on the expected fully burdened cost of manufacturing qualifying vaccine products (without recapture of research and development costs) (the "**Manufacturing Cost**").

Schedule B to Draft Term Sheet for Framework Agreement (HIV/AIDS)

Criteria for Termination of Funder's Payment Obligations

[*Insert*]

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Term Sheet for an Advance Market Commitment

Guarantee & Supply Agreement

1. Parties: Funder(s) and one or more Designated Suppliers.[21]

[21] The Framework and Guarantee Agreement term sheets are designed to accommodate a variety of sponsors, despite the fact that there are substantial differences between governmental and nongovernmental organizations in areas such as funding capacity and ability to contractually commit to the Guarantee Agreement. The Guarantee Agreement term sheet permits a single Funder, multiple Funders or a system where a lead Funder parcels out participations to sub-Funders.

2. Purpose: Guarantee that the Designated Supplier(s) receive a specific price[22] for each sale of the Approved Vaccine if the sale qualifies as a Qualified Sale (as defined below) and the Approved Vaccine is purchased for use in an Eligible Country (as defined below), provided that the Designated Supplier commits to supply the Approved Vaccine to Eligible Countries as provided herein.[23]

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[22] The Guarantee Agreement provides for a price guarantee, rather than a minimum quantity guarantee. The Guarantee Agreement is designed so that price for each Qualified Sale could vary. For example, a higher payment could be made in the early years to permit the Developer to recapture R&D costs and capital investments in manufacturing capacity more rapidly, with lower payments in the later years.

Because Developers are ultimately driven by profits, rather than sales, the anticipated cost of goods will be an important factor for any potential Developer in deciding whether to participate in the Framework. Notwithstanding the total size of the Maximum Guaranteed Amount, if the price per Dose is low (*i.e.,* the Maximum Quantity is high) relative to the anticipated cost of goods, then the Developer will not likely be motivated to participate in the Framework. The risks for the Developer are both that the Maximum Guaranteed Amount will not generate a sufficient return on its investment and that, once the guarantee has been exhausted, it will be obligated to supply at the Ongoing Supply Price for a loss.

As discussed in note 9, the Framework mitigates some of the risk of high cost of goods for the Developer with respect to the ongoing supply price, by permitting the Committee to adjust upwards the Ongoing Supply Price Ceiling. The Guarantee Agreement also alleviates some of the risk with respect to the Guaranteed Price by automatically adjusting the Guaranteed Price to reflect changes in the Ongoing Supply Price and therefore the Minimum Co-Payment. In other words, the Funders' financial commitment, or top up, under the Guarantee Agreement with respect to each course of treatment remains fixed, but the Guaranteed Price (*i.e.,* the total payment to the Designated Supplier) varies. For example, if the initial Guaranteed Price of $24 is based on an initial Minimum Co-Payment of $6, then the Funders would be obligated to pay $19 per course of treatment, regardless of any change to the Minimum Co-Payment, but the Guaranteed Price paid to the Designated Supplier would change based on changes to the Minimum Co-Payment (which would result from changes to the Ongoing Supply Price). So, if the Ongoing Supply Price increased (*e.g.,* as a result of higher than anticipated Manufacturing Costs), the Guaranteed Price would increase.

Alternatively, the Guaranteed Price could be fixed, so that the payment to the Designated Supplier would be set and the financial commitment of the Funders would change based on changes to the Minimum Co-Payment. For example, if the initial Guaranteed Price of $24 is based on an initial Minimum Co-Payment of $6, then the Designated Supplier would receive $24 per course of treatment, even if the Ongoing Supply Price, and therefore the Minimum Co-Payment, changes. In this scenario, the Guaranteed Price would not increase to reflect increased Manufacturing Costs, but the amount that the Funders would be obligated to contribute to the Guaranteed Price would be decreased based on an increase to the Ongoing Supply Price and, therefore, an increased Minimum Co-Payment. Similarly, a reduction in the Ongoing Supply Price would decrease the Minimum Co-Payment, subject to the Minimum Base Price, and, therefore, increase the amount that the Funders would be obligated to contribute to the Guaranteed Price.

[23] Vaccine must be made available to all Eligible Countries on a first-come, first-served basis. A Developer could not select a few Eligible Countries where it wishes to offer the vaccine. Moreover, as discussed below, a Developer may not cease to supply vaccine once the price guarantee is exhausted.

3.	**Principal Responsibilities of Funder:**	Guarantor will, subject to Sections 7 and 13 below, irrevocably and unconditionally Guarantee that the [gross] price paid to a Designated Supplier will be not less than the price set forth in Schedule A (the **"Guaranteed Price"**) for each Qualified Sale of the Approved Vaccine up to the maximum number of sales specified in Schedule A (the **"Maximum Quantity"**);[24] provided that (a) the Base Price is not less than the greater of the Base Price Minimum and the Ongoing Supply Price Ceiling (as each may be adjusted from time to time pursuant to the Framework Agreement) (the **"Minimum Co-Payment"**), and (b) the Approved Vaccine is purchased for use in an Eligible Country. The **"Base Price"** is the amount actually paid, directly or indirectly, by the purchaser of the Approved Vaccine.[25]

[24] The Maximum Quantity and the Guaranteed Price can be set to yield desired revenue. Price guaranties are on a per treatment—*e.g.*, course of immunization—basis, rather than a per dose basis.

[25] The Minimum Co-Payment concept, together with the Minimum Base Price floor, was introduced to create an incentive to help ensure that qualifying vaccines are not wasted and that payments are not made for unusable vaccines. If countries, or other donors, are required to make a minimum investment in an Eligible Vaccine, then there is greater likelihood that appropriate quantities of the vaccine will be procured and that those quantities will be administered. This also provides additional safeguards that donor funds will not be wasted on a vaccine for which there is no market. Given the current state of research, it is likely that an AIDS/HIV vaccine may take many years and may utilize as yet unidentified technology. Intervening events, such improvement in treatment options or the development of entirely new vaccine technologies, may render a technically adequate vaccine unnecessary or unattractive. Similarly, unforeseen characteristics of an Approved Vaccine, such as medically harmless but culturally unacceptable side effects, which would not have been addressed in the technical specifications, may render an otherwise safe vaccine unsuitable in certain countries. The co-payment requirement helps ensure that the advance market commitment will be used for Approved vaccines that actually meet the requirements of the Eligible Countries.

4.	**Principal Responsibilities of Designated Supplier:**	The Designated Supplier will (a) use commercially reasonable efforts to create awareness of the availability of the Approved Vaccine in the Eligible Countries in order to meet the public health requirements in the Eligible Countries,[26] (b) establish manufacturing capacity for the production of the Approved Vaccine to meet the public health requirements for the Approved Vaccine in the Eligible Countries as provided in Section 9,[27] (c) obtain and maintain World Health Organization (WHO) prequalification (or any substitute qualification determined by the Committee) for the Approved Vaccine,[28] and those facilities used in its production, as well as any local authorizations and approvals necessary to market and sell the Approved Vaccine in the Eligible Countries, including by complying with all adverse event reporting requirements and providing ongoing evidence of product and production safety and regulatory compliance, (d) provide the Committee with copies of all written communications to or from, including all filings or submissions to, and summaries of all oral communications with, the WHO or any other relevant regulatory agency with respect to the Approved Vaccine, (e) in connection with the marketing, distribution and sale of the Approved Vaccine, comply with the U.S. Foreign Corrupt Practices Act and all other applicable law,[29] (f) provide information as reasonably requested by the Committee from time to time in order to confirm ongoing compliance with the technical specifications and usability requirements set forth in Section 8 of the Framework Agreement, (g) agree to be bound by decisions of the Committee acting within

[26] Although the Designated Supplier has responsibility for generating awareness of the availability of Approved Vaccines in Eligible Countries, Funders must also share in this responsibility.

[27] It is critical that the Designated Supplier have adequate manufacturing capacity to meet the ongoing needs of the Eligible Countries, not just the Maximum Quantity of product. In addition, as noted below, consideration needs to be given to the contract remedy if the Designated Supplier fails to establish adequate manufacturing capacity, or otherwise meet its supply requirements, under the Guarantee Agreement, particularly once the Guaranteed Price has been exhausted. Section 15 of the Guarantee Agreement includes a proposal for liquidated damages, but other options are available.

[28] Because it would be extremely costly to create an Independent Assessment Committee that is fully capable of evaluating, approving and monitoring the Eligible Vaccines and their ongoing production, the Framework and Guarantee Agreements permit the Committee to rely on third parties and their procedures, such as the WHO and its pre-qualification process.

[29] Compliance with the Foreign Corrupt Practices Act was imposed to alleviate concern that illegal payments might be used to generate demand. Obviously, the purpose of the Advanced Markets mechanism is to generate orders for vaccines that will be used, not to simply to generate orders for vaccines.

the scope of its authority,[30] and (h) continue to supply product to Eligible Countries to meet their requirements as provided in Section 8.

5. Qualified Sale: The sale of the Approved Vaccine for use in an Eligible Country will be deemed a **"Qualified Sale"** if it meets the criteria set forth in Schedule B, as modified from time to time by the Independent Assessment Committee. In the event of a conflict between a Contract Administrator or a Funder and the Designated Supplier over whether a particular sale of the Approved Vaccine satisfies the criteria for a Qualified Sale, the matter will be resolved by arbitration.

6. Eligible Countries: Each of the countries listed in Schedule C will be deemed **"Eligible Countries"**). Schedule C may be revised from time to time by the Independent Assessment Committee in order to (a) add countries that have (i) per capita GDP (as determined by World Bank) of less than $1,000 or (i) per capita GDP equal or greater than $1,000 but less than $5,000 and adult prevalence of HIV/AIDS that is greater than 5%, or (b) remove countries that have (i) per capita GDP equal to or greater than $5,000 or (ii) per capita GDP less than $5,000 but equal to or greater than $1,000 and adult prevalence of HIV/AIDS less than or equal to 5%.

The GDP thresholds will be adjusted from time to time to reflect adjustments made by the World Bank in its definition of low income countries.

7. Cap on Total Commitment [and Termination of Commitment]: The total payment obligation of Funder pursuant to the Guarantee and Supply Agreement, including all payments and distributions to the initial Designated Supplier and any additional or replacement Designated Suppliers, will (a) not exceed, in the aggregate, [$3.6 billion] (the **"Maximum Guaranteed Amount"**), and (b) be subject to termination or modification by the Independent Assessment Committee pursuant to Section 22 of the Framework Agreement. [Schedule C of the Framework Agreement sets forth the assumptions underlying the calculation of the Maximum Guaranteed Amount and the criteria for adjusting it if the number of Eligible Countries is materially reduced or a *force majeure* event occurs.]

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[30] There is a tension between the need for certainty in the determinations of the Independent Assessment Committee and the need for some review. Court review was deemed impractical in most circumstances. Instead, the goal is to create an Independent Assessment Committee that would be viewed as independent and impartial by all participants in the Framework, but which is subject to review if it exceeds or abuses its authority, and with respect to certain critical decisions, such as a decision to alter or terminate the Funders' payment obligation in the face of a force majeure event, as described in note 37 below.

8. Supply

The Designated Supplier will supply the Approved Vaccines in Eligible Countries as provided herein during the Funding Term (as defined in Section 12) and, thereafter, for a period of ten (10) years, or such longer period as the Designated Supplier may determine (the "**Supply Term**"), at a price not to exceed (a) if the Designated Supplier has received total payments for the sale of the Approved Vaccine in Eligible Countries under the Guarantee Agreement together with the Base Price (the "**Gross Sales**") in amounts, in the aggregate, greater than fifty percent (50%) of the Maximum Guaranteed Amount (the "**Minimum Gross Sales Amount**"), then the Ongoing Supply Price Ceiling, and (b) if the Designated Supplier has not received such amount, the Ongoing Supply Price Ceiling will be increased by fifty percent (50%) only until the aggregate Gross Sales for the Approved Vaccine equals the Minimum Gross Sales Amount, whereupon the increase in this clause (b) will cease to apply. [31]

Each Designated Supplier will be obligated to supply sufficient quantities of Approved Vaccine to meet the demand for such Approved Vaccine in the Eligible Countries based on a forecast to

[31] The Guarantee Agreement requires that the Developer continue to make Approved Vaccines available even after the Funding Period expires at a price not to exceed the Ongoing Supply Price Ceiling. If there are multiple Developers, the Ongoing Supply Price Ceiling will be increased for a limited time for any Developer that does not receive a certain minimum percentage of the Maximum Guaranteed Amount during the Funding Term, which amount is defined as the Minimum Gross Sales Amount. The increase will cease to be effective, and the cap will return to the predetermined amount, once the Developer's aggregate sales equal the Minimum Gross Sales Amount. The Minimum Gross Sales Amount is intended to be a rough proxy for a return on the Developer's investment in the Eligible Product, but cannot exceed 100% of the Maximum Guaranteed Amount. The cap will be set forth in technical specifications in Appendix A to the Framework Agreement, and may be modified, in the discretion of the Independent Assessment Committee, as provided in Section 10 of the Framework Agreement.

[32] Because it will be difficult to establish the supply requirements in advance, the Guarantee Agreement provides that the Designated Supplier and the Contract Administrator will agree on a forecast. However, a Designated Supplier may be concerned that the Contract Administrator would establish aggressive supply requirements that would not be realized. As an alternative, the Guarantee Agreement could provide a mechanism for the Parties to determine an appropriate forecast or this could be referred to the Committee or an independent expert. Another option would be for the Funders to guarantee the forecast or a portion thereof in addition to the price. While this would shift some risk to the Funders, the forecast would be established once the Approved Product had obtained regulatory approval.

[33] The capacity requirements are designed to permit a Designated Supplier to establish capacity to supply Approved Vaccine outside the Eligible Countries without unfairly diverting such supply from the Eligible Countries. Other metrics could be used to provide similar protection, such as requiring that a Designated Supplier establish a dedicated facility to supply Approved Vaccine for Eligible Countries.

be reasonably agreed to by such Designated Supplier and the Contract Administrator from time;[32] provided that in no event will a Designated Supplier be obligated to establish more manufacturing capacity to meet such forecast than it would for a comparable product with a similar market potential, which market potential shall be based on the Guaranteed Price and the Maximum Quantity; and provided further that a Designated Supplier shall not decrease such capacity (including by diverting Approved Vaccine for use outside Eligible Countries) after the Funding Term below its peak capacity during the Funding Term.[33] Notwithstanding the foregoing, a Designated Supplier will be relieved of its obligations with respect to an Approved Vaccine under this paragraph if, at any time after the third anniversary of the launch of such Approved Vaccine, the actual demand for such Approved Vaccine in the Eligible Countries is less than ten percent (10%) of the forecasted demand (other than as a result of a breach by such Designated Supplier of its obligations under the Guarantee and Supply Agreement).[34]

9. Intellectual Property: The Designated Supplier will own all right, title and interest in and to the Approved Vaccine; provided, however, if the Designated Supplier fails to supply Approved Vaccine in the Eligible Countries as required in Section 8 during the Funding Term or the Supply Term or if the Designated Supplier meets such supply obligations, but such supply is not sufficient to meet the forecasted demand in the Eligible Countries and, in any event, within four (4) years prior to the expiration of the Supply Term, the Designated Supplier will grant Funder, or its designee, a non-exclusive, irrevocable, perpetual, license (with the right to sublicense) to make, have made, use, sell, offer for sale and import the Approved Vaccine solely for use in any Eligible Country, but Funder will not have rights to any other products and will have no right to sell Approved Vaccine outside the Eligible Countries or for use in the military or travelers markets in Eligible Countries. The Designated Supplier will provide such technology and material transfer and technical assistance as may be reasonably requested by the Funder to transfer the manufacturing process for the Approved Vaccine to the Funder or its designee. The license grant will be royalty-free, unless the Designated Supplier has not been paid the Minimum Gross Sales Amount and is not in breach of the Guarantee and Supply Agreement, in which case such grant will be subject to a royalty of [__] percent of net sales until such time as the aggregate royalty payments to the Designated Supplier equal the product of (a) [__] percent, multiplied by (b) the amount, if any, by which the Minimum Gross Sales Amount exceeds the aggregate Gross Sales

[34] This provision is included to protect Designated Suppliers in the event that forecasted demand for an Approved Vaccine is not realized.

of the Approved Vaccine, whereupon such vaccine will be fully-paid and no further royalties will be due.[35]

10. Representation and Warranties: The Guarantee and Supply Agreement will include customary representations and warranties for suppliers of pharmaceutical products, including conformity with product specifications and regulatory approvals, manufacturing in accordance with current good manufacturing practices or other applicable standards, and lack of infringement of third party intellectual property rights.

11. Indemnification and Insurance: The Designated Supplier will defend and indemnify the Funder, the members of the Independent Assessment Committee, or the applicable institution, and the Contract Administrator(s) from all claims and losses arising out of or related to (a) the use of the Approved Vaccine, including claims and losses for physical or mental injury (including death) and (b) infringement or misappropriation of intellectual property.[36] Each Designated Supplier will maintain such type and amounts of liability insurance, including, if appropriate, through a risk retention program, as is normal and customary in the industry generally, which will specifically cover the foregoing indemnification obligations.

12. Term: The Guarantee and Supply Agreement will begin on the date that the Committee designated the first Approved Vaccine and continue through such time as the Maximum Guaranteed Amount has been paid (the **"Funding Term"**), and, thereafter, until the end of the Supply Term, unless earlier terminated pursuant to Section 12.

13. Termination: The Guarantee and Supply Agreement may be terminated by either party in the event of a material breach that is not cured within 30 days of notice thereof from the non-breaching party.

In addition, Funder will have the right to terminate the Guarantee

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[35] If the Designated Supplier of an Eligible Vaccine fails to meet its supply requirements under the Guarantee Agreement, it would be required to grant the Funders, or their designee, a non-exclusive, royalty-free (except as necessary to provide the Designated Supplier with the Minimum Gross Sales Amount, as described above) license to exploit the Eligible Vaccine only in Eligible Countries. Although less than ideal, this is intended to make the relevant technology available to the Funders if the Designated Supplier breaches its obligations under the Guarantee Agreement. Because this provision may not provide much of an incentive not to breach, especially if a Designated Supplier has already received the Maximum Guaranteed Amount and because, even with this license, there could be a disruption of supply, the term sheet also includes a liquidated damages provision in Section 15.

[36] Indemnification is deemed to be particularly important to attract qualified members to serve on the Independent Assessment Committee. It is contemplated that this indemnification would be similar to that which is provided for directors and officers of corporations.

and Supply Agreement (a) with respect to a particular Designated Supplier in the event the Independent Assessment Committee determines that the Approved Vaccine of that Designated Supplier no longer satisfies the technical specifications and usability requirements set forth in Section 8 of the Framework Agreement, or (b) in the event of a force majeure event as determined by the Independent Assessment Committee as set forth in Section 22 of the Framework Agreement.[37]

14. Addition of New Designated Suppliers: If the Independent Assessment Committee determines that a newly developed vaccine satisfies the conditions precedent in Section 7, subject to Section 10 of the Framework Agreement, and the Developer of the newly developed vaccine elects to become a party to the Guarantee Agreement, the Developer of the new vaccine will be deemed a "Designated Supplier", the new vaccine will be deemed an "Approved Vaccine" and the new Designated Supplier will have the right to compete with the original Designated Supplier to make Qualified Sales of the new Approved Vaccine in the Eligible Countries under the Guarantee Agreement. The addition of new Designated Suppliers and Approved Vaccines will, in each case, be subject to the cap on Sponsor's total commitment set forth in the Section 7.

15. Remedies in the Event of Breach: The parties will have the right to pursue all available contract remedies, including damages, specific performance and other equitable relief. In addition, if a Designated Supplier fails to meet its supply obligations with respect to an Approved Vaccine, other than as a result of a *force majeure* event, the Funder will be entitled to receive as liquidated damages, and not as a penalty, an amount equal to Gross Sales of Doses of Approved Vaccine for which payments were made under the Guarantee Agreement, less the Base Price.

16. Dispute Resolution: [Arbitration under AAA rules in NY, NY.]

17. Governing Law: [New York law.]

18. Waiver of Immunity: If the Funder is a sovereign, it will (a) acknowledge that the

[37] A *force majeure* provision permitting the Independent Assessment Committee to alter the Guarantee Agreement based upon extraordinary events has been included. The force majeure clause would permit the Committee to void or alter the Guarantee Agreement in the event of major changes to technology or disease epidemiology that render a vaccine either inappropriate or unnecessary. For example, if advances in other technology substantially reduced the incidence or transmission of HIV/AIDS in Eligible Countries, then the Funders financial obligation would be reduced accordingly. As noted in Section 7 of the Guarantee Agreement term sheet, Schedule C [would include] [includes] criteria, such as assumptions underlying the Framework Agreement, to guide the Independent Assessment in taking any such extraordinary action, which as noted in the Framework Agreement term sheet, would be subject to judicial review.

transactions are subject to private commercial law, and (b) waive sovereign immunity.

19. Other Provisions: Other covenants, terms and provisions as requested by legal counsel to Funder or the Designated Supplier.

Schedule A to Draft Term Sheet for Guarantee and Supply Agreement

Guaranteed Price and Maximum Quantity

A. Guaranteed Price.

The Guaranteed Price is $24, and is based on an assumed Minimum Co-Payment of $6. If the Minimum Co-Payment is changed (as provided in the Framework Agreement), then the Guaranteed Price will be adjusted upwards or downwards by adding an amount equal to the adjusted Minimum Co-Payment less $6. By way of example, if the initial Guaranteed Price is $24 and the Minimum Co-Payment is (1) increased to $8, then the Guaranteed Price will be increased by $2 ($8 minus $6) or (2) decreased to $1, then the Guaranteed Price will be decreased by $5 ($1 minus $6).

C. Maximum Quantity (of vaccine in Doses). 200 million.

Schedule B to Draft Term Sheet for Guarantee and Supply Agreement

Criteria for Qualified Sales

A. Buyer Criteria.

1. Buyers Included. Qualified Buyer include (a) UNICEF, (b) WHO, (c) Pan American Health Organization, (d) any individual Eligible Country that is purchasing for the benefit of the public sector or local non-profits, and (e) and any other buyer approved by the Independent Assessment Committee.

2. Buyers Excluded. A pharmaceutical company, acting directly or indirectly thorough one or more intermediaries, will not qualify as a Qualified Buyer.

B. Sales Criteria.

1. Course of Treatment. A single course of treatment, regardless of the number of individual immunizations, required to provide the desired efficacy and duration of protection will be deemed a single "Dose" and will constitute a single sale. For example, if three immunizations over a period of 2 years are required to achieve the desired efficacy and duration of protection, then the sale of all three immunizations, one Dose, will be required to constitute a Qualified Sale.

2. Bundled Sales. In the event that the Designated Supplier bundles the sale of the Approved Vaccine to a purchaser with the sale or licensing of another product or service of the Designated Supplier or its affiliates, the Designated Supplier will reasonably assign prices to (allocate revenue amounts between) the Approved Vaccine and such other products or services sold or licensed by the Designated Supplier or its affiliates to the purchaser, in accordance with the terms set forth in Exhibit B1 in order to ensure that the Designated Supplier has attributed a reasonable and equitable portion of that sale to the Approved Vaccine.

3. No Top Up. The Designated Supplier will not seek or receive any additional compensation or value for the sale of the Approved Vaccine in an Eligible Country other than compensation from the purchaser in the form of the Base Price and the compensation from the Funder under the terms of the Guarantee and Supply Agreement; provided, however, that the Designated Supplier may seek and receive additional compensation or value if (a) additional Funders are added to the Guarantee and Supply Agreement by amendment, or (b) approved by the Contract Administrator, or its designee, in writing.

4. Use in an Eligible Country. If the Approved Vaccine is purchased for use in a particular Eligible Country, the Designated Supplier must have a reasonable expectation that the Approved Vaccine will actually be used in such Eligible Country. For purposes of illustrating the foregoing, if UNICEF, as it presently operates, certifies that a country has certain requirements for the Approved Vaccine, then the Designated Supplier will have a reasonable expectation that such requirements of the Approved Vaccine will actually be used in such country.

C. <u>Other Criteria</u>.

[*Insert other criteria*]

* * *

Schedule C to Draft Term Sheet for Guarantee and Supply Agreement

Eligible Countries

[*Insert list*]

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Annex 2. List of firms consulted

Name of company	Date interviewed	Participants
Acambis	May 27, 2005	**Clement Lewin** Vice President, U.S. Government Affairs and Strategy
Alloy Ventures	May 27, 2005	**J. Leighton Read** General Partner
AlphaVax	May 27, 2005	**Peter Young** President & CEO
Avant Immunotherapeutics	May 27, 2005	**Una Ryan** President & CEO
Nektar Therapeutics	May 27, 2005	**Rob Chess** Chairman
SG Cowen	May 27, 2005	**Stelios Papadopoulos** Vice Chairman
Serum Institute of India	June 3, 2005	**S.V. Kapre** Executive Director **S.S. Jadhav** Executive Director, Quality Assurance and Regulatory Affairs
Bavarian Nordic	June 7, 2005	**Peter Wulff** President and CEO **Paul Chaplin** Chief Scientific Officer
Targeted Genetics Corporation	June 7, 2005	**Stewart Parker** President and CEO
Bio-Manguinhos/ FIOCRUZ	June 8, 2005	**Akira Homma** Director **Ricardo Galler**
Crucell	June 9, 2005	**Jaap Goudsmit** Chief Scientific Officer **Arthur Lahr** Vice President, Business Development **Govert Schouten** Senior Director, Business Development
Chiron Vaccines	June 30, 2005	**Dan Soland** President **Rudi Daems** Executive Director, Policy and Corporate Affairs **Anthony Lakavage** Director, Corporate Public Policy
sanofi pasteur	July 1, 2005	**Beth Waters** Senior Vice President, Communications **Joel Calmet** Director, Public Policy **Allan Jarvis** Senior Vice President, Corporate Development
GlaxoSmithKline Biologicals	July 20, 2005	**Deborah Myers** Director, External and Government Affairs and Public Partnerships **Walter Vandersmissen** Director, Public Partnerships

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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 23 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI's financial and in-kind supporters include the Alfred P. Sloan Foundation, the Bill & Melinda Gates Foundation, The New York Community Trust, The Rockefeller Foundation, The Starr Foundation; the Governments of the Basque Country, Canada, Denmark, European Union, Ireland, The Netherlands, Norway, Sweden, United Kingdom, and United States; multilateral organizations such as The World Bank; corporate donors including BD (Becton, Dickinson & Co.), Continental Airlines, DHL and Pfizer; leading AIDS charities such as Broadway Cares/Equity Fights AIDS, Crusaid, Deutsche AIDS-Stiftung, and Until There's A Cure Foundation; other private donors such as the Haas Charitable Trusts; and many generous individuals from around the world. For more information, see www.iavi.org.

IAVI-New York
110 William Street
New York, NY 10038
United States

IAVI-East Africa
Floor 16, Rahmutulla Tower
Upperhill Road, PO Box 340
Nairobi, Kenya

IAVI-Europe
Postbox 15788
1001 NG, Amsterdam
The Netherlands

IAVI-India
193 Floor 4, Jorbagh
New Delhi, 110003
India