Preliminary Report

How can public-private partnerships accelerate the availability of vaccines for the developing world?

July 2001

This paper is intended to promote discussion of issues, and does not represent the views of the World Bank.

EXECUTIVE SUMMARY

Public and private sector partners in the Global Alliance for Vaccines and Immunization (GAVI) are committed to ensuring that priority vaccines are rapidly developed and made available to children in the poorest countries.

GAVI partners believe that they can best achieve their objectives by not only strengthening and expanding the delivery of existing vaccines, but also by harnessing the complementary expertise of both public organizations and private firms. The GAVI Board has mandated that partners move the public-private discussion from rhetoric to action, identifying and addressing the scientific, financial, logistical, and policy hurdles currently blocking the rapid development and use of new vaccines in the developing world.

Public-private partnerships can only work if two basic conditions are met. First, both partners must understand the costs, risks and benefits driving the partnership. With this knowledge, partners can identify those costs and risks that are important and sensitive to public sector support --- those with the highest "leverage". Second, both partners must be confident that the mechanisms or agreements which define the partnership protect each of their interests. For the public sector this means ensuring public investments result in more rapid development, expanded capacity and/or lower prices. For the private sector it means public "promises" translate into real financial commitments, minimizing the risk of late stage "changes of heart".

This preliminary report outlines a generic framework for disaggregating and evaluating these costs and risks. The tentative findings in this paper must be validated through detailed analysis with public and private partners. It is clear that the costs, risks and benefits will vary given a vaccine's stage of development and target market. However, certain general findings offer interesting insights into the potential of partnerships. For example, the study highlights three key leverage points and then identifies specific public-private interventions that might address these points and thereby impact the availability of vaccines.

- **Reducing the R&D risk, particularly additional clinical trials**: The study estimated that clinical trials may, in fact, represent the single largest incremental cost faced by a manufacturer bringing a global vaccine to the developing world. Trials are also higher risk as these sunk costs are not flexible or recoupable (unlike investment in, for example, a piece of equipment). Given their cost and risk, trials are often a "go/no go" decision point for manufacturers, and can be a pivotal hurdle in the corporate decision-making process. While industry expects to bear much of the R&D risk, this incremental cost and the extra risks it entails are high and sensitive to public sector support. Direct financing to strengthen trial infrastructure and finance trials is likely to be a cost-effective use of public funds.

- **Overcoming manufacturing capacity constraints**: The increase in demand for vaccines and the growing range of new products are increasing competition for both existing and new production capacity. In addition, new regulatory pressures are limiting the flexibility of capacity. The opportunity cost of supplying low-income countries has increased, as new capacity decisions for these vaccines must compete against higher margin products. Without public sector support for capacity expansion, many vaccines may not be developed or adequately scaled-up. Mechanisms that provide specially designed grants, low-cost loans or loans with repayment conditional on uptake or profitability, may be valuable.
- **Minimizing or eliminating the demand risk**. There is tremendous uncertainty about whether a sufficiently large market will ultimately exist to justify the up-front investments required to develop each vaccine. At present, vaccine manufacturers are expected to bear the majority of the demand risk. However, the public sector has the capacity to control this risk through mechanisms that stimulate demand, strengthen delivery infrastructure and guarantee purchase.

These preliminary findings are based on a brief study by McKinsey & Company which drew on publicly available information and high level interviews. This study is only the first of many steps needed to meet the GAVI challenge. It is hoped the general framework outlined in this paper will provide a useful platform for more detailed discussions with the potential developers and suppliers of near term priority vaccines such as Meningococcal A/C conjugate, pneumococcal conjugate, rotavirus and DTP-based combinations. The ultimate objective of this work is for public and private partners to jointly develop proposals that highlight more efficient ways to manage and share costs and risk, enabling GAVI to ensure that the world's priority vaccines are available to developing countries.

PRELIMINARY REPORT: HOW CAN PUBLIC-PRIVATE PARTNERSHIPS ACCELERATE THE AVAILABILITY OF VACCINES TO THE DEVELOPING WORLD?

INTRODUCTION

The introduction of cutting-edge vaccines and the creation of new vaccines for the developing world have been very slow (see Exhibit 1) for a variety of reasons. On the part of the public sector[1], financing constraints, low political visibility for preventive services and weak delivery systems have all contributed to the slow uptake of existing vaccines into national immunization schedules. In addition, concerns about the profit incentives motivating private industry have made the public sector wary of partnering with firms for the supply of new products. On industry's part, the historical unwillingness to pay for vaccines, reinforced by the relatively small and uncertain revenues for "traditional" vaccines[2], have made vaccine makers wary of investing in the development and production scale-up of new vaccines for developing country markets.

Accelerating the development, scale up and use of priority vaccines for developing countries will require significant effort from all the partners in the Global Alliance for Vaccines and Immunization (GAVI), ranging from governments in developing and industrial countries, WHO, UNICEF, the World Bank, foundations, private industry and others. Among this broad spectrum of partners, there is increasing consensus that an opportunity exists to break the historical patterns and behaviours, and move the discussion on public-private partnerships from rhetoric to action.

Public-private partnerships can only work if two basic conditions are met. First, both partners must understand the costs, risks and benefits driving the partnership. Second, both partners must be confident that the mechanisms or agreements which define the partnership protect each of their interests. For the public sector this means ensuring public investments result in more rapid development, expanded capacity and/or lower prices. For the private sector it means public "promises" translate into real financial commitments, minimizing the risk of late stage "changes of heart".

As a first step, the GAVI Financing Task Force, through the World Bank, commissioned McKinsey & Company to explore the basic foundation of public-private partnership. This included building a broad understanding of the incremental risks and costs of rapidly developing and producing vaccines for developing countries, identifying the key leverage points sensitive to public intervention, and assessing the relative effectiveness of different innovative finance mechanisms designed to share costs and risks.

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[1] In this context, the definition of the "public sector" is not restricted to government, but encompasses a broad range of institutions and agencies, including philanthropic foundations, academic institutions, multi- and bilateral development agencies. In contrast, the "private sector" referred to in this report encompasses for-profit vaccine makers

[2] Traditional vaccines include DTP, TT, BCG, OPV, measles and hepatitis B

This paper, which is based on work undertaken by McKinsey & Company, outlines preliminary findings and suggests how this thinking might be validated and used to develop into concrete public-private partnership proposals.

The findings are presented in three parts. In Section 1, we outline the approach to disaggregating risks and costs in order to identify promising points of leverage, where public-private partnerships can potentially have a large positive impact. In Section 2, we describe and assess a set of possible finance mechanisms, and indicate which of them is most likely to work for specific types of products. In Section 3, we propose steps to apply this conceptual work on public-private partnerships, and to generate "win-win" deals. The methodology underlying the work is presented in Annex 1. Various relevant exhibits (referred to within the text) are included in Annex 2.

WHAT DOES RISK HAVE TO DO WITH VACCINE AVAILABILITY?

Mature and efficient markets always fully price risk. High-risk investments have high but unpredictable returns, while low risk investments tend to have low, but reliable returns. For vaccine development, investment in high-risk vaccines facing scientific or market uncertainty should be balanced by higher prices for the finished product. Investments in low-risk vaccines where the science is known, the development is straightforward, and/or the market is guaranteed, should result in lower price products. In reality, producing any vaccine has some risk, the questions are how large is the risk, what drives this risk, and who takes or pays for it.

If public organizations carry little or no risk in the development or scale-up of a vaccine, all the risk is left to the private firm. Firms may choose to minimize the risk by slowing down or even stopping their investment in a vaccine's development. If the firm goes forward, it may translate the risk into higher prices once the product is available. Both of these responses—slow development and high prices—have affected the availability of vaccines which are of great interest to the developing world.

Taking the other extreme, the public sector could carry all the risk. It could be entirely responsible for the development and commercialization of the vaccine—in practice, however, this approach has rarely proved successful. The public sector institutions involved in vaccine R&D are primarily focused on basic science knowledge diffusion, rather than single-mindedly solving applied development problems to ensure large scale, consistent production. The incentives in the public sector reinforce this knowledge focus and are generally inconsistent with efficient production of commodities.

By engaging in carefully structured partnerships, the risk equation can be changed; the public sector can share risks with the private firms and thereby change the firm's behavior. For example, guaranteeing a minimum purchase, and thereby reducing the firm's uncertainty about demand would lower the risks and should lead to lower costs (see Exhibit 2).

In considering the potential for public-private partnerships, it is useful to recognize two factors. First, risks inherent in the development, manufacturing and pricing decisions may not be fully understood by partners in either sector. Second, partners may not price the same risk equally. Together, these factors create opportunities to enhance collaboration, namely:

- Improving the transparency of decision making by clearly outlining the risks and behaviors that drive vaccine costs, particularly the:
  - Incremental costs of accelerating vaccine availability from industrialized to developing markets (for example, for pneumococcal conjugate, rotavirus, and some HIV vaccines)
  - Costs and risks incurred for vaccines developed specifically for developing country markets (for example, for meningococcal A conjugate, and vaccines against *shigella dysenteriae* and HIV strains that predominate in developing countries).
- Identifying areas where the public and private sectors can alter traditional risk sharing schemes to mutual benefit—"win-win" arbitrage opportunities where one partner can reduce the risks (and therefore costs) of the other at relatively low cost to itself.

Public-private partnership may result in a shift down the current risk-cost curve. Sharing or eliminating risk may induce firms to develop and/or scale-up production more quickly, or price vaccines more cheaply. Even more exciting is the possibility that public-private partnership may actually accelerate the development **and** reduce a product's net cost by more efficiently allocating risk.

SECTION I: UNDERSTANDING INCREMENTAL COSTS AND RISKS

DISAGGREGATING THE COSTS

Understanding the economic factors associated with making a vaccine available to the developing world depends on understanding the specific costs and risks. The general framework outlined in this paper attempts to capture all relevant risks and costs, breaking costs out in three different ways:

- First, the framework explores costs and risks associated with the different links of the vaccine value chain—R&D, manufacturing, scale-up, regulatory management, distribution, pricing and expected returns, and demand (see Exhibit 3).
- Second, costs and risks are categorized into those that are directly product-attributable and those that are not. Costs associated with clinical trials for a specific vaccine, for example, are attributable, while the costs of other unsuccessful vaccine candidates are not. Both types of costs are real and are borne by the manufacturer and thus must be factored into the estimates (see Exhibit 4).
- Third, in cases where the vaccines have both industrial and developing country markets, only the incremental costs associated with developing country supply are explored. For vaccines intended exclusively for developing country markets, the entire cost and risk chain needs to be analyzed to identify opportunities.

IDENTIFYING AND QUANTIFYING INCREMENTAL COSTS AND RISKS

The relative costs and the pricing of risks vary significantly by the type of vaccine, the status of the research, the manufacturing technology and the target market. Assuming that more of the costs and risks of a "global" vaccine are passed on to the customer in the industrial country market, the incremental cost of supplying the developing world are much lower. More detailed analysis is needed to accurately estimate the incremental risks and costs for specific vaccines. However, as an illustrative example, the team explored a semi-hypothetical case of a vaccine being tailored for developing country markets.[3] Rough estimates of the major costs and risks (see Exhibit 5) showed half of the costs were directly attributable to the vaccine (e.g. R&D, raw materials, royalties, administrative and management costs) and half were associated with risks inherent in developing and selling the product. Costs are explored both as lump investments and on a per dose basis assuming the successful development and production of the product.[4]

[3] These estimates are loosely based on the development of meningococcal A/C conjugate, a vaccine that would use existing knowledge (based on the development of meningococcal C) but requires significant new investment in R&D and scaling-up to serve the developing country market. The findings should be roughly generalizable.

[4] This semi-hypothetical case assumed 250 million doses over several years.

The different risks and their relative importance include:

- **R&D.** The risk of failing to develop a workable vaccine that meets the market's requirements is estimated to account for approximately 20% of the cost[5] over the development span of the product. McKinsey noted that the pharmaceutical industry's growing sophistication in identifying indicators of low risk, successful R&D projects is offset by the increasingly stringent regulations and higher expectations from the public sector.
- **Clinical trial.** The calculated risk of clinical trials failing or delaying the launch of the vaccine is estimated at between 7-12% percent of costs. In addition, the cost of supplemental clinical trials required for each geographic region was estimated to add some $0.04 to $0.05/dose to the cost of the vaccine per health region covered (e.g. $7 to $11 million per trial in Africa, Asia, or Latin America).
- **Incremental regulatory approval.** This cost is limited and provides an example of where the public sector has attempted to reduce risk in a "win-win" manner. For a cost recovery fee of only US$17,000 per annum per product for initial assessment, and $2,500 for reassessment, the World Health Organization (WHO) mitigates incremental regulatory risk for manufacturers of traditional vaccines by providing regulatory "approval in principle" for purchase by United Nations agencies. Many developing countries choose to use this list to guide national licensing. However, the WHO assessment does not actually substitute for national registration by any country and so does not replace all regulatory expenditures.
- **The cost of additional capacity.** This will vary by manufacturer and depend on the ability to share existing capacity. Due to current global capacity constraints and increased regulatory pressures which limit facility sharing, additional capacity will likely be required for this vaccine.
- **Liability risk.** The risk of litigation due to adverse reactions to the vaccine is not costed here. The cost of this risk can be quite substantial but does not apply in most markets. In the U.S. particularly, the current management of liability risk, in fact, reflects an effective "win-win" collaboration between the public and the private sector. To limit private litigation that threatened to make the supply of vaccines uneconomical, the US government set up the injury compensation trust fund to address claims. Many European and developing countries have reduced the liability risk (and thus the associated cost) altogether through legislation. However, some manufacturers believe the increasing levels of litigation highlight that the compensation systems remain sub-optimal in some European markets and most developing countries.

[5] Cost in this case refers to the cost of all of the components that go into vaccine research and development and is not limited to a specific timeframe.

- **Demand risk and expected returns.** The costs created by the uncertainty of demand, the dependence on a highly concentrated group of purchasers, and the opportunity cost of using limited staff, equipment and capital for a vaccine with only a developing country market (as opposed to a vaccine with an industrial country market) represents one of the largest cost components— roughly 13-20 percent of the cost. The **potential cannibalization of prices** that may result from offering a lower price to developing countries is one of the most frequently cited risks. Despite the concerns, the risk and thus the cost for vaccines (unlike drugs) is almost nonexistent due to closely controlled distribution chains. This is evidenced by the independent development of dramatically different price points for Hib vaccines in the US versus PAHO countries (see Exhibit 6). A second example is the increasing, rather than decreasing, spread in price for Hep B vaccine in the US and developing countries. While cannibalization is therefore not an issue in vaccines, the existence of different price points does create a number of risks and costs, which have not been quantified yet:
  - **Political risk.** Past Congressional pressure on US vaccine makers for using tiered prices, for example, has resulted in a historical reluctance for US-manufactured vaccines to be supplied to developing markets at prices below US CDC contract rates.
  - **Developing countries' middle market risk**. Many developing countries have significant private healthcare markets comprised of the wealthier populations. Hypothetically, providing a low-cost vaccine to the public sector in developing countries could undermine these private, higher price markets for vaccine makers. The evidence to date indicates that this risk may not be as large as anticipated as both the products and distribution channels are differentiated for the private market. For example, a significant price difference exists between United Nations-purchased Hep B vaccine in India and Brazil and the branded equivalent (see Exhibit 7).
  - **Opportunity cost.** The opportunity costs inherent in limited capital, limited staff and constrained capacity will also be incurred by manufacturers developing and delivering products to the developing country markets. For example, lowest income developing countries have historically only borne prices of less than US$0.10 per dose and middle income countries have borne $1-2 per dose, whereas industrial countries have purchased vaccines at price points of US$5-50 per dose Today, the public sector typically bears little risk in the commercialization and provision of vaccines (with the exception of the investment in basic research which is pre-product and the share of the liability risk as discussed above) leaving the private sector to bear all of it. Based on the preliminary findings of this study, such a traditional "risk sharing" arrangement for a vaccine requiring investment to tailor it to developing countries—such as meningococcal A/C conjugate vaccine—would

result in a decision by firms to either not invest in the product or require a market price possibly in excess of US$20 per dose. While this price may be sustainable for industrial countries, it is outside the reach of developing countries.

This preliminary analysis suggests that if the public sector bore or eliminated much of the risk, developing country-specific vaccines could be developed and supplied rapidly and at a significantly lower price per dose. There are significant opportunities for “win-win” interventions.

SECTION II: INNOVATIVE PUBLIC-PRIVATE INTERVENTIONS

The concept of public-private partnership to accelerate the development and supply of vaccines to the developing world has been widely discussed in recent years. This concept builds on the relatively long history of collaboration between public sector immunization partners and the vaccine firms (see Exhibit 8). However, the traditional approaches are proving inadequate to address the increasing risks and costs associated with the ambitious GAVI objectives.

A range of market interventions have been identified as possible ways to cost-effectively overcome barriers facing different vaccines (see Exhibit 9). These interventions are often classified into "pull" (e.g., market guarantees) and "push" strategies (e.g., reducing the required investment). The section briefly profiles the various alternative finance arrangements.

- **R&D [push mechanisms]**
  - **Development grants and loans** repayable once a product achieves commercial success.
  - **Public sector labs** and research facilities to reduce absolute R&D costs.
  - **Sponsorship of specific clinical trials** to reduce the cost of trials and accelerate time to market.
  - **Investment in strengthening trial infrastructure** to reduce the cost and risk of failure in trials, and to improve the credibility of trial data for licensure applications
  - **Tax credits** to stimulate R&D in selected areas.
- **Production scale-up [push mechanisms]**
  - **Capital loans** for infrastructure and scale-up to overcome current capacity shortage and reduce the crowding out from alternative capital uses. These loans can be made repayable once the produce achieves commercial success.
- **Manufacturing [pull mechanisms]**
  - **Improved order behavior** (in particular, earlier and more accurate demand forecasting) to smooth demand volatility and thus reduce peak manufacturing capacity and the cost of manufacturing (which needs lead time as long as 9-15 months).
  - **Guaranteed mid-/long term purchase contracts** to create incentives for large-scale infrastructure investment.

- **Regulatory management [push mechanisms]**
  - **Public sector influence** to harmonise, standardise, enforce TRIPS[6] and accelerate registration.
  - **Public sector expertise** to increase the likelihood of meeting license requirements and reducing risk of failure.
  - **Regulatory patent protection** to create incentives for focused investments.
- **Pricing and demand [pull mechanisms]**
  - **Volume and price guarantees** to eliminate demand uncertainty.
  - **Public sector advocacy** to stimulate local demand and thus reduce demand uncertainty.
  - **Strengthening delivery infrastructure** to ensure that latent demand can be satisfied and uncertainty reduced.
  - **Direct demand stimulation** to pre-agreed minimum purchase levels (e.g., through financed or subsidized purchases).
  - **Tiered pricing** to bring forward and support developing countries' market demand while supporting the systems to maintain separate price points for wealthier markets.
  - **Tax credits on vaccine sales** to increase the effective price to manufacturers of vaccine sold to developing countries.
  - **Patent extensions or transfers** to reduce the opportunity costs of developing country supply.

IDENTIFYING THE LEVERAGE POINTS AND HIGH IMPACT INTERVENTIONS

The potential effectiveness of each intervention depends on both the value of the intervention to vaccine manufacturers and the ability of the public sector to implement it easily and cost-effectively (see Exhibits 10 and 11). As already highlighted, the value depends on the specific vaccine's stage of development and target market. Continuing with the semi-hypothetical example, meningococcal A/C conjugate builds on the licensed meningococcal C conjugate product but still requires significant investment to tailor it to developing country needs. For this example, interventions addressing the uncertainty of future demand, the moderate capital costs required to expand capacity and high R&D risk stand out as potentially being both high-value and cost-effective (see Exhibit 12).

[6] Agreement on Trade Related Aspects of Intellectual Property Rights

The preliminary findings of this study indicate that several interventions represent true "win-win" opportunities. These opportunities are likely to be cost-effective for the public sector—in other words, each dollar invested by the public sector in these interventions leads to better health in the countries through more rapid availability and affordable pricing of priority vaccines. At the same time, these interventions are also likely to be attractive to the private sector as they create incremental direct profit opportunities (through market growth and development) and indirect profit opportunities (through better leverage of technology, or use of dormant patents, etc).

Demand guarantees: reducing the market uncertainty

There is tremendous uncertainty about whether a sufficiently large market will exist once investments are made. The lack of a credible market significantly increases the scale-up, capacity expansion and profit risks. Price is only one variable affecting demand. Even when vaccines are provided at zero price (i.e., financed by donor agencies), the historical uptake of new vaccines by developing country governments has been highly variable (see Exhibit 13) and often surprisingly low.

Demand guarantees require a multi-pronged approach that includes stimulating demand in developing markets, strengthening vaccine delivery infrastructure and, at least in the short-term, guaranteeing future purchase of the product.

Implementing demand guarantees may represent a significant "win-win" opportunity. McKinsey estimated that guarantees have the potential to reduce the total cost—and price—of making a vaccine available to developing countries by 10 to 15 percent, while simultaneously enhancing the overall attractiveness of the vaccine market.

- **Purchase guarantees** would reduce the manufacturer's risk of investing in research and equipment that might end up idle. A number of manufacturers noted, for example, that the lack of long-term purchase guarantees by UNICEF, coupled with unpredictable demand, significantly increased their risk of capital expansion. The value of this intervention to vaccine makers is high due to the constraints on existing capacity and the significant risk of expansion. The cost to the public sector is low if existing funds can provide a credible commitment. However, implementing this mechanism may prove to be difficult due to the public sector's inability to effectively prioritize and secure limited public sector funds, and the high opportunity cost if the public sector must do more than promise future funds. Additionally, the question of how to manage situations in which key specifications change in the period between agreement and delivery has not been resolved, which increases risk for both the public and private sectors.
- **Advocacy, demand stimulation and delivery infrastructure** are complementary initiatives targeted at reducing demand risk. These activities include advocacy programs and disease burden studies that inform policy makers within developing

country markets of the local burden of disease. Using public sector resources for these activities is attractive because they directly address larger public health objectives and ensure a delivery pipeline for future vaccines. The public sector is uniquely positioned to strengthen access as it has the relationships and technical and systems knowledge needed by governments.

Scale-up subsidies

Growth in global demand for vaccines, increased regulatory pressures and the growth of new combination products are reducing available capacity. The opportunity cost of supplying developing countries has increased because new capital allocation decisions for these vaccines must compete against higher margin products. Vaccine manufacturers interviewed highlighted that without public sector support for capacity expansion, many vaccines are unlikely to be rapidly developed or introduced into developing country markets. Alternative finance mechanisms to address this challenge include:

- **Grants or low-cost loans.** Public sector support of scale-up and capacity expansion either through grants or low-cost loans will reduce the opportunity cost of capital. Making the repayment conditional on the profitability of the vaccine may make these grants or loans even more attractive. The arbitrage opportunity and the expected impact of this intervention may be smaller than demand guarantees. However, the current capacity constraints facing the vaccine industry make this a "make or break" for many manufacturers and therefore a highly valuable "win-win" intervention:
  - It is of high value to vaccine makers because it lets them eliminate significant capital outlays with uncertain return.
  - It is easy to implement and practical because the manufacturer's incentives for efficient resource management continue to be aligned through ownership of the asset.

R&D support

For vaccines that still require significant development and testing, public sector R&D support provides a very important leverage point. The nature of the support will vary significantly based on the level of development of the vaccine. Clinical trials are probably the single largest incremental cost item for global vaccines tailored to developing country markets, though, depending on the number of doses produced they may represent a very small percentage of the total cost of developing a successful vaccine. For a vaccine whose proof of product is established in industrial countries, grants or loans that support **strengthening clinical trials infrastructure** and **additional trials** may represent a "win-win" arbitrage opportunity to reduce the cost of establishing the efficacy in developing countries.

DIFFERENT OBSTACLES, DIFFERENT SOLUTIONS

The three interventions discussed above are likely to be effective for most vaccines that are well along the path toward global commercialization. A number of other interventions have considerable merit for vaccines facing different obstacles to development or production (see Exhibit 14).

- For vaccines still in research phase (e.g., HIV vaccine), a possible intervention is **R&D investment in early stage research and clinical trials.** Rather than demanding the traditional equity stake, the return on this investment could be defined in terms of low-cost access into developing country markets. By funding higher risk, early stage research, the potential ability of the public sector to affect price is great. The International AIDS Vaccine Initiative (IAVI) is testing this strategy in its funding of HIV vaccine research. IAVI, in effect, is using its resources as venture capital to drive the commercialization of research mainly through small biotech start-ups. Equity returns are foregone in return for a guarantee to supply the developing country market at cost-plus (actual costs plus a pre-agreed "profit" margin) once the market is developed. IAVI's actual ability to "collect" on its investment is not yet known. Not only is cost-plus open for interpretation, but IAVI may be negotiating with a different firm if the biotech or its patent has been purchased by the time the product is commercialized.
- There are a growing group of licensed vaccines that are demanded in the developing country markets but no longer used in industrial country markets (e.g. all combination vaccines including a whole-cell pertussis component). The shift from having a global product to only a developing country product is changing the risks, costs and benefits for each manufacturer. Maintaining adequate capacity to serve the developing country markets is becoming an increasingly important issue. **Capacity grants/loans to producers** or the **provision of networks to facilitate technology transfer** to developing country producers may be useful interventions. For example, vaccines based on the Diphtheria-Tetanus-Pertussis (DTPw) platform[7] formerly served a global market. Many industrial countries have now switched to an acellular form of pertussis vaccine, while developing countries continue to use the much cheaper and equally effective whole-cell pertussis. Some manufacturers are either completely discontinuing their production of whole-cell pertussis and its combinations, or are limiting or not expanding supply. The result is a current shortage of some DTPw combination vaccines, like DTPw-Hep B[8] for use in developing countries.

[7] DTPw, DTPw-Hib, DTPw-HepB, DTPw-Hib-HebB, DTPw-IPV

[8] However, for other DTPw combination vaccines like DTPw-Hib, Unicef noted that it did not see enough demand to justify entering into long-term purchase agreements, so there is excess capacity.

- While regulatory hurdles are not a major risk or cost as compared with the others highlighted in this paper, the ability for the public sector to **overcome individual regulatory hurdles** is a key arbitrage opportunity. For example, a dengue vaccine for the developing country market is currently under development at Aventis. By helping to define the optimal licensing route, the public sector could help to avoid costly regulatory steps.

SECTION III: A WAY FORWARD

This study is only the first of many steps needed to meet the GAVI challenge. Using readily available data and qualitative information derived from interviews with knowledgeable sources, McKinsey has tried to approximate the potential value of public-private opportunities—"win-win" arrangements for both sectors—and to understand their relative effectiveness. It is hoped the findings of this work will provide a useful platform for more detailed discussions with the potential developers and suppliers of near term priority vaccines such as meningococcal A/C conjugate, pneumococcal conjugate, rotavirus and DTPw-based combination vaccines.

The ultimate objective of this work is for public and private partners to jointly develop and implement proposals that highlight more efficient ways to manage risks. Thus enabling public and private partners in GAVI to ensure that the world's priority vaccines are available to developing countries.

Based on the feedback from public and private partners, the GAVI Financing Task Force hopes to design a more in-depth effort to work closely with individual manufacturers to explore not hypothetical cases, but real problems constraining the work on priority vaccines (see Exhibit 15). Ideally, this follow-on work would result in detailed proposals for public-private partnerships; outlining the incremental costs, the benefits to the public and private partners, and steps for the implementation of specific finance mechanisms.

MOVING ON: PUBLIC-PRIVATE PROPOSALS

Individual firms will be asked to express interest in developing a proposal, with the expectation that some (but not all) of those proposals would lead to public-private partnership deals. Interested firms would work with GAVI partners through a mutually trusted third party (i.e., technical consultants such as McKinsey) to develop joint proposals for specific vaccines, exploring:

- Disaggregating the incremental risks and costs to develop and scale-up the production of a target vaccine(s) for developing country markets;
- Identifying promising interventions, based on an understanding of the risks and costs;
- Arriving at a realistic value for the various "push" or "pull" interventions (e.g., estimating how much a purchase guarantee is worth to a specific manufacturer for a particular product);
- Based on those estimates, identifying the finance mechanisms with the greatest leverage (e.g., most impact for least effort or money from the public sector).
- Tailoring and implementing the public-private agreement to align incentives (e.g., for efficient behaviour) and appropriately compensate each partner for the portion of risk that they assumed.

The products of this work would be a set of detailed firm-specific proposals for accelerating the supply of priority vaccines to developing country markets. These proposals will build on the prioritized scientific, technical and commercial actions identified as on the product's critical path. Given the commercially sensitive nature of the data, confidentiality of any material developed would have to be assured. At the same time, efforts would be made to share more general knowledge developed through this process—for example, what alternative finance mechanisms tend to work in certain settings—to better inform the broader community.

Evaluating the Proposals. Mobilizing its unique combination of expertise, the "Out of the Box" group-- a strategic and high-level working group of 10-12 individuals (see Annex 3) from the worlds of finance (in the public and private sectors), development agencies, the pharmaceutical industry and philanthropic foundations, would review aspects of the proposals and provide advice to the GAVI partners. The group members, brought together in their individual capacities under the auspices of GAVI, will bring a unique set of skills to the immunization community, including a better understanding of the economic and financial motivations and markets, the creative powers to break out of old molds, and the personal and institutional credibility to lead others to adopt new strategies. Out of the Box will be asked to advise on possible financing mechanisms, the viability of specific proposals, the longer-term and non-financial impact of different finance arrangements, and the "fit" of the proposals with the overall goals of GAVI partners.

This work would continue until the most promising partnership ideas had been thoroughly and systematically analyzed and vetted. In the unlikely event that none of the proposals bore fruit, this work would still dramatically move forward the dialogue and debate about ensuring the rapid availability of vaccines to children of the developing world. In the best case scenario, the end product of this work would be firm agreements between specific vaccine makers and GAVI partners (and/or other stakeholders), including dollar amounts, timetables and contingency arrangements.

APPENDIX 1:

STUDY METHODOLOGY

This initial study comprised three steps:

- **Refining the approach.** The analysis began by identifying the discrete components of risk. Building on the previous work by the World Bank and Mercer Management on the hurdles and incentives affecting investment in an HIV/AIDS vaccine, the team interviewed a range of healthcare experts and vaccine manufacturers to understand generic risk categories, and biases the public and private sector have toward bearing these risks (i.e., their relative pricing of the risk).

- **Applying the approach to a specific vaccine**. In a second step, these generic risk categories were applied to specific vaccines that are targeted to developing countries. The team used existing data to quantify and ultimately price the various risks "outside-in", validating the directional data through interviews with public and private experts. The analysis focused on the incremental costs of adapting and supplying an existing vaccine to developing country markets, and on understanding other financial and non-financial barriers (e.g., capacity constraints). The result of this step was an understanding of the cost/risk chain and an identification of key leverage points where potential win-win opportunities may exist.

- **Identifying the relative effectiveness of alternative finance mechanisms**. In the final step, the alternative finance mechanisms were assessed based on the magnitude of addressed risks/cost, and the ease and cost of implementing each possible intervention.

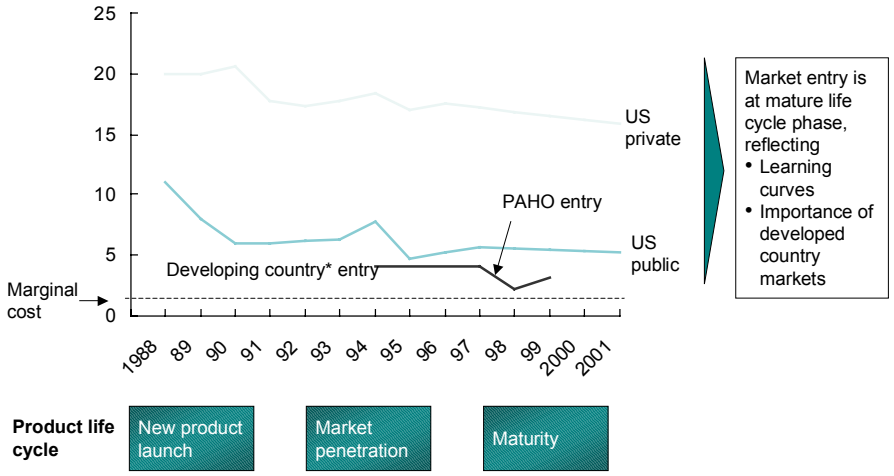
The methodology has both strengths and weaknesses. It is limited by dependence on interviews and qualitative information, rather than detailed quantitative data about a full range of possible vaccines and finance options. At the same time, however, it benefits from the participation of both industry and non-industry experts on vaccines and their markets. In addition, the work is enriched by McKinsey and Company's breadth of knowledge about pharmaceutical and other related industries and markets.

ANNEX 2.

Exhibit 1

VACCINE LIFE CYCLE—HIB EXAMPLE

$/dose

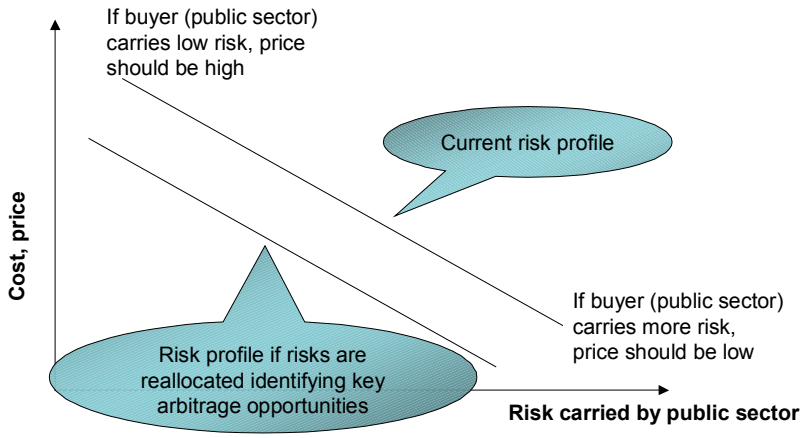


* Latin American country's purchase for private and public markets (not including Pan American Health Organization (PAHO) regional bulk purchase)

Source: PAHO; CDC: Interviews

Exhibit 2

RISK AND OPPORTUNITY COST PRICING



Source: Team analysis

Exhibit 3

IDENTIFYING RISKS ALONG THE VALUE CHAIN

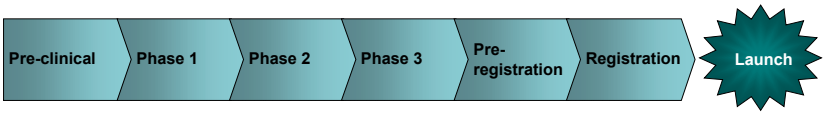
Risks

Baseline	1. Market exists with acceptable volume and prices	3. Proof of product (in one market) Clinical dev i. Safety ii. .Immunogenicity iii. Efficacy iv. Effectiveness	5. Fixed cost production capacity scale-up (volume assumption) – Scale effects – Site	6. Marginal cost of production – Learning curve – Scale	7. Approval – Cost – Time – Probability of success	8. Distribution	9. Expected rate of return
Incremental for developing country markets	2. Developing country demand exists	4. Proof of product in additional targeted markets					10. Risk of cannibalization

Exhibit 4

VACCINE DEVELOPMENT COSTS: Average per product

1996*/2000 Estimates



Time	2.4	2.0	1.8	1.4	1.1	1.3	Total 10 years
Market entrance probabilities Percent	22%	39%	54%	68%		98%	
Number of candidates in pipeline*	4.6	2.5	1.9	1.5		1***	
Cost of drug development/ candidates** $ Million	8.5	12.0	33.0	39.0			
Cost of vaccine development/ candidate Year 2000 $ Million	5–7	6–9	37–68	46–48		30–40***	

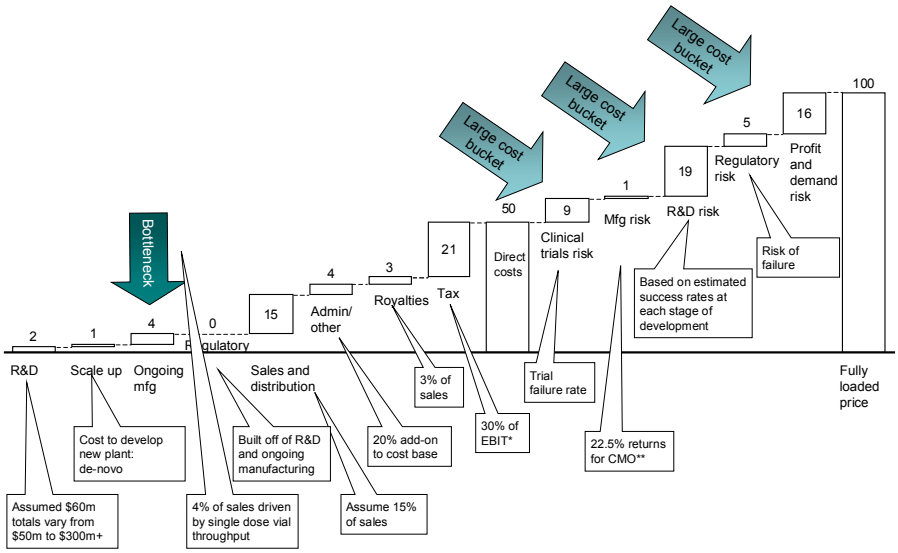
* n=591 candidates between 1993 and 1994
** For large pharmaceutical firms $>360 million sales
*** Additional post marketing trials has increased regulatory and licensing costs in line with Phase 3 trials
Source: Vaccine; Vol. 14 pp. 1,301–1,302, 1998 (Mark Struck—Head of Regulatory Affairs): Pharma interviews

Exhibit 5

BASE COSTS: Generic Vaccine

INDICATIVE

Cost per dose as a percent of sales

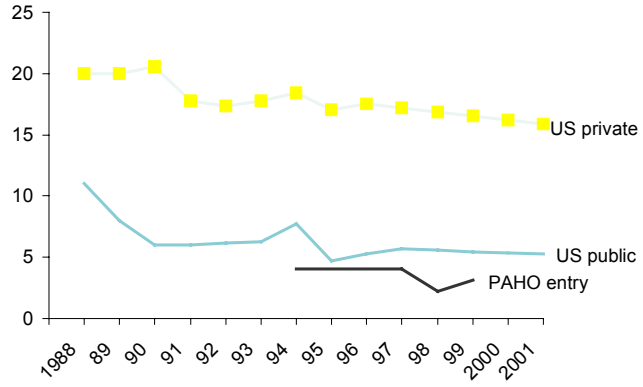


Source: Interviews; team analysis * EBIT – Earnings Before Income Tax ** CMO – Contract Management Organizations

Exhibit 6

PRICE OF HIB VACCINE: PAEDIATRIC DOSES 1989–2001

2001 US $ per dose

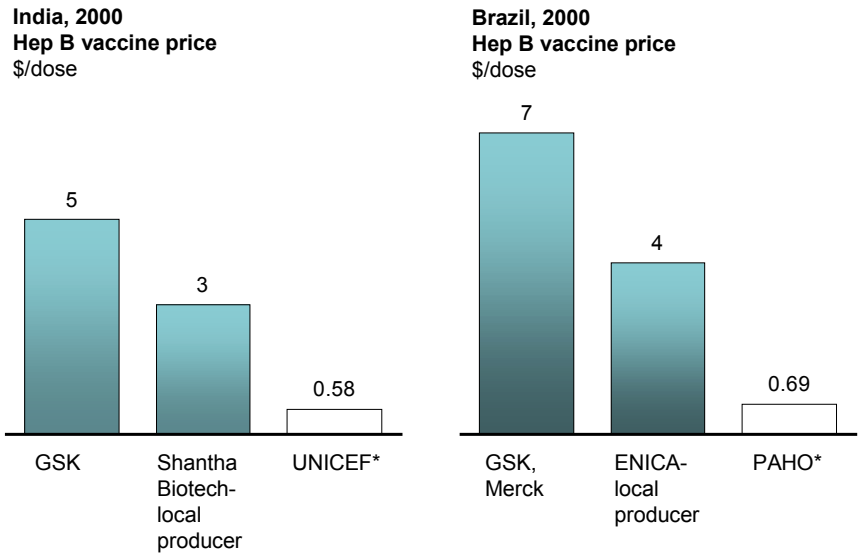


* Prices prior to PAHO procurement in 1998 are from Latin American country uptake

Source: CDC; NIAID

Exhibit 7

LDC MARKET PRICE TIERING



* 1999 prices

Source: McKinsey India; McKinsey Brazil

Exhibit 8

PUBLIC SECTOR INTERVENTION ALREADY UNDERTAKEN

EXAMPLES

	Intervention	Trade-offs
Demand and profit	• CDC contracts Aventis to meet 9.9 million dose influenza vaccine shortfall (2000) • CDC contracts manufacture of smallpox vaccine	• CDC covers production cost for 9.9 million doses at $3/dose • If demand is not met, Aventis has right to sell to private sector at $5/dose • Guarantees purchase in return for production • Company retains right to sell to more profitable markets
R&D risk	• GSK co-develops malaria vaccine with significant public sector support	• GSK validates valuable technology platform • Public sector gets big pharma product development skills
Liability risk offset	• US government creates National Vaccine Compensation program funded by federal excise tax on vaccines to offset vaccine manufacture liability risk – 1970s US vaccine manufacturers threaten to cease vaccine production due to excessive potential liability claims – $3 billion of liability against $6M in sales forces 7 of 9 DTP producers to exit	• Take on US vaccine manufactures liability risk in return for vaccine manufacturers staying in the industry

Source: Interviews

Exhibit 9

FINANCE MECHANISMS BY STAGE OF VACCINE DEVELOPMENT AND MARKET

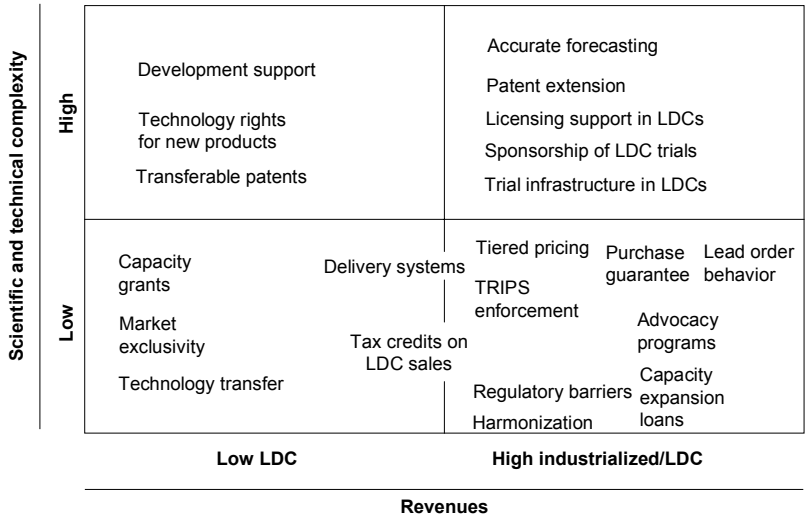


Exhibit 10

ISSUES RAISED ABOUT INTERVENTIONS

	Intervention	Issues raised in interviews
R&D	• Technology rights	• 'Joint technology developed with public sector must stay with pharma' • Very little IP comes from public sector
Manufacturing scale-up	• Grant/payment for capacity	• Prefer to free loans to grants as some manufacturers did not want 3rd party ownership of capacity
Manufacturing on-going	• Transfer of technology rights	• Unlikely intervention as – Takes 5–6 years to transfer technology – Most countries can't get scale of large pharma – Production know-how is core proprietary IP only to be transferred under majority JVS
Regulatory	• Harmonization • Fast track	• 'Nice to say, tough to do' • Not feasible due to significant regulation hurdles
Distribution	• Distribution -- delivery infrastructure • Creating demand through advocacy	• This should be a key priority for local organizations • Very little work has been done to date on prioritizing vaccines by need and the country's ability to absorb new vaccines—this should be 1st priority
Demand and profit	• Purchase guarantees	• Past track record of lack of long-term purchase guarantees is no longer acceptable • Doubts as to public sector's ability to make long range guarantees of 5 yrs+
	• Tiered pricing • Patent extensions/high levels of transferable patents	• Not currently an EU problem, but if it does raise it's head, industry expects public sector support • Real skepticism about public sector's ability to implement • Risk of reward for vaccine going elsewhere

Source: Interviews

Exhibit 11

INTERVENTION OPPORTUNITIES

Key barrier

	Interventions	Value to pharma	Size of arbitrage opportunity	Ease of implementation
R&D	• Development grants	◑	●	◑
	• Technology rights—1st right of refusal for high value markets	◑	◔	○
	• Create infrastructure for clinical trials	◑	●	◑
	• Sponsor clinical trials	●	●	●
Manufacturing scale-up*	• Grants **or**	◑	◑	●
	• Loans/investment with payment contingent on pharma ability to secure secondary, profitable markets	◕	◑*	●
Manufacturing ongoing	• Outsource technology to LDC	○	◔	○
	• Improved lead order times	◕	●	○
Regulatory	• Licensing and recommendations support	●	●	●
	• Overcoming individual regulatory hurdles (eg,EU whole cell pertussis issue)	●	●	◑
	• Harmonization	●	●	○
Distribution	• Delivery system development	●	●	◑
Demand and profit	• Accurate forecasting	◑	◔	○
	• Advocacy programs	◕	●	◑
	• Demand guarantees—purchase guarantees	●	●	◑
	• Patent extensions/transferable patents**	◑	◑	○
	• LDC market exclusivity for 5 years**	●	◑	○
	• Reinforce tiered pricing	●	◑	○
	• Tax credits on LDC sales	●	○	○

● High
◑ Medium
○ Low

* Value where market inefficiencies exist due to informational arbitrage opportunities
** Pharma believes this is not realistic that the public sector can do this
Source: Interviews

Exhibit 12

CURRENT BARRIERS TO ACCELERATED ENTRY INTO LDC MARKETS

	Barriers	Examples	Importance Pharma	Importance Public **
R&D	• Lack of commitment for specific project support from public sector • R&D pipelines are currently full	• 'Public sector often acts as disinterested, third parties'	M	L–M
Manufacturing scale-up*	• No excess capacity • Unwillingness to commit to capacity without public sector assistance for low margin products • Regulatory complexity means scale effects less significant	• Lack of long term forecasting makes capacity expansion risky • Industry takes on capacity expansion risk without firm UNICEF orders	H	L–M
Manufacturing ongoing	• Technology capability transfer to LDC is costly and has risks	• Technology transfer to LDC nations is risky and can take up to 5–6 years • Some industrial manufacturers transfer technology in majority JVs only • Domestic production is often sub-scale	L–M	H
Regulatory	• Complex cumbersome LDC regulations • Regulatory pressures are driving up costs	• PAHO requires additional summary protocals over other UN agencies • Manufacturers spend up to 30–40 days per annum on plant inspections • EU rules limit licensing LDC products	L	L–M
Distribution	• Lack of delivery infrastructure	• Many countries only reach 30-60% of target population	M–H	M–H
Demand and profit	• Lack of clear public sector requirements • Great uncertainty about demand coupled with low margins • Risk of changing public sector mandates • US political disincentives for LDC price tiering	• Lack of prioritization given disease burden and existing programs • Lack of confidence in public sector forecasting • Lack of confidence that the public sector will purchase products declared "priority"	H	H

Key barrier
L - Low
M – Medium
H - High

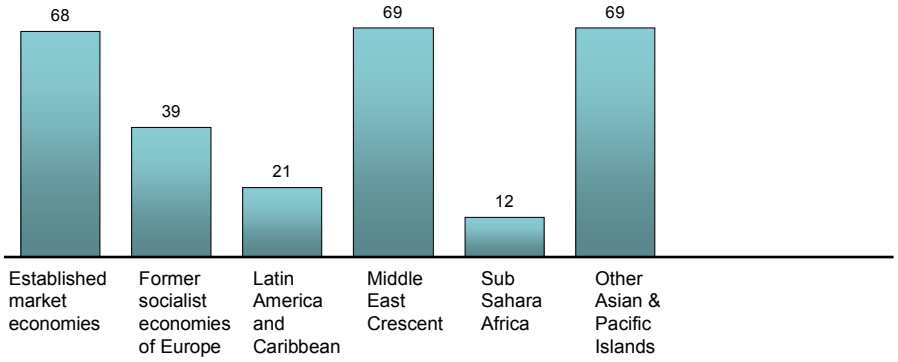
* Rated as opportunity cost
** Interviews with staff in Centers for Disease Control, WHO, World Bank, and others
Source: Interviews

Exhibit 13

DIFFERENT REGIONS AND NATIONS HAVE DIFFERING VACCINE UPTAKE RATES

Frequency of adoption of HB into routine vaccination schedules, October 1998

Percent of nations*



* 179 countries studied

Source: Mark Miller: Vaccine 2000

Exhibit 14

OBSTACLES TO PRODUCT DEVELOPMENT

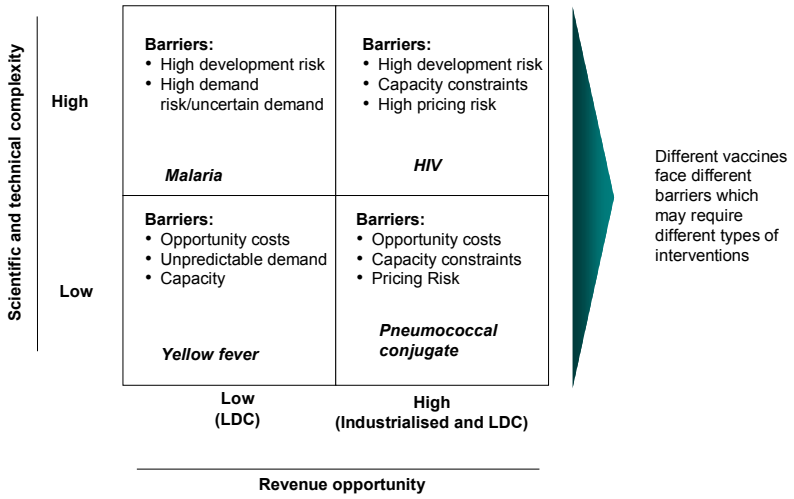
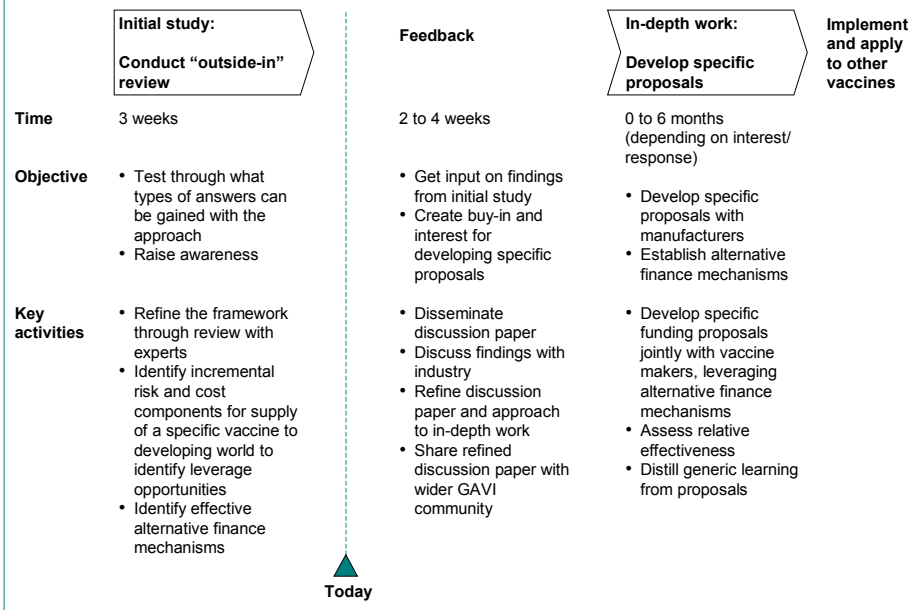


Exhibit 15

PROJECT APPROACH



ANNEX 3.

"OUT OF THE BOX" GROUP MEMBERS

1. Dr. Matthias Bekier, Principal, McKinsey & Company
2. Dr. Seth Berkley, President and CEO, International AIDS Vaccine Initiative
3. Mr. G. Stephen Burrill, CEO, Burrill & Co.
4. Dr. Mohamed A El-Erian, Managing Director, Pacific Investment Management
5. Dr. A. Richard Jefferson, Executive Director and
   Chief Research Scientist, Cambia
6. The Honorable Dr. Katele Kalumba, Minister of Finance of Zambia
7. Mr. Paul Klingenstein, General Partner, Aberdare Ventures
8. Mr. Geoffrey Lamb, Director, World Bank
9. Ms. Patty Stonesifer, Co-chair and President, Bill and Melinda Gates Foundation
10. Sir Richard Sykes, Non-executive Chairman GlaxoSmithKline