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Key Stakeholders and Funding of HIV and Malaria Vaccines: Considerations in selecting appropriate instruments for accelerating the public health impact of vaccination in poorer countries

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Key stakeholders and funding of HIV and malaria vaccines: Considerations in selecting appropriate instruments for accelerating the public health impact of vaccination in poorer countries

Executive Summary

Future preventive vaccines for HIV and malaria sit within a broad array of opportunities for addressing the diseases associated with poverty that adversely affect the health and economic development of developing countries. The opportunities to control infectious diseases of poorer countries through vaccination include ones which would be achieved with currently **'under-used vaccines'**, recently licensed (**'recent'**) **vaccines**; **late development-stage vaccines**; and **early design/development-stage vaccines**. The latter category includes those for HIV, malaria, tuberculosis and various other diseases.

Recent scientific reviews suggest that the main current challenge in developing an ultimately useful, adequately effective, and safe vaccine for HIV/AIDS or malaria is generating a body of knowledge that can guide successive design of hopefully more effective candidates.¹ Since immunity from natural infection does not occur (HIV) or is weak and poorly understood (malaria), this knowledge will probably come from taking risks on many different prototype candidate products in early clinical trials.

The fastest route to defining an effective HIV or malaria vaccine suitable for wide use in developing countries is likely to be the simultaneous testing of a wide array of possible product designs – a so-called portfolio – deriving from research institutes, biotechs, product development partnerships (PDPs) and large R&D-based vaccine companies. Tools that facilitate comparison of the performance of candidates (assays, standards, consensus on trial end-points, clinical trials and regulatory capacities in disease endemic countries, etc.) all play an important part in accelerating early stage vaccine development. These design and comparison tools have been identified as current major needs in HIV and malaria vaccine development. (See footnote.)

The ultimate useful design will probably require successive improving 'generations' of vaccines. When, and where, to implement partially effective vaccines poses significant policy, strategy, and procurement questions, particularly where there may be difficult to resolve safety questions.

Clearly the time frame for vaccine development, typically a dozen years at least with a further dozen years at least to achieve wide use, also means some benefits from vaccination could be achieved sooner than with early development-stage vaccines. This does not mean that products which are further back in the development pipeline should not receive attention – rather they should receive the attention that is most likely to accelerate their progression to use.

The steps of development and introduction through which the various candidate vaccines for all diseases progressively pass are largely similar. (Figure S.1) Often the early parts of this progression entail multiple feedback loops, as the scientific community as a whole learns what makes a more effective candidate product. These steps, and the progression of candidate vaccines, are embedded within a broader 'system' of supportive capacities and coordination. This 'system' must also be adequately financed and optimized for the timely

¹ Consultations on the Global HIV Vaccine Enterprise (<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=544553>) and the Malaria Vaccine Technology Roadmap (<http://www.malariavaccineroadmap.net/roadmap.html>)

identification, comparison, development, supply and utilization of what ever product/products is/are deemed to possess adequate efficacy and safety for use to combat any given disease.

It is desirable to address issues in introduction of vaccines into developing countries early as historically this has been subject to unnecessary delays. These have arisen variously from poor disease burden estimates (Hib), failure to plan for financing (HB), failure to project demand (combinations), and failure to address strategy safety issues (rubella).

Accelerating vaccine development and introduction for use in developing countries is receiving increased attention after a lengthy period (of around 3 decades) in which the overall commercial pharmaceutical industry became less enthusiastic on vaccines in general and even more so with respect to vaccines to be used predominantly in poorer developing countries. This lack of enthusiasm arose for many reasons but primarily because there existed (and still exist) more commercially attractive opportunities in the general pharmaceutical field.

The author estimates that in 2004 the global pharmaceuticals market amounted to US\$ 550 billion (IMS data); the global market for vaccines about US\$ 7.0 billion at most (up from US\$6.0 billion in 2000, Mercer Management Consulting estimate); and the market for (all) vaccines to the poorer developing countries at most US\$ 0.5 billion (up from US\$220 million in 2002, UNICEF data). The largest selling individual vaccine (recently licensed Prevnar® for pneumococcal pneumonia) has estimated sales of over US\$ 1.0 billion, mostly in the USA. 'Blockbuster' drugs on the other hand can individually generate annual sales of US\$ 5.0 billion or above and large pharmaceutical companies may nowadays be uninterested in products with sales less than US\$ 500 million (up from \$ 300 million in 1997 as estimated by Mercer Management Consulting).

Paradoxically over the same 3 decades scientific advances led to increased understanding of diseases and new 'tools' that could be applied to design of candidate vaccines. These developments in the biotechnology sphere also led to new players – small biotech companies – that are contributing significantly at the early stages of vaccine development. Most do not have manufacturing experience but their existence – and the emergence of vaccine producers in advanced and large developing countries, coupled with so-called public-private partnerships for product development (or product development partnerships, PDPs) may provide alternative pathways for development and supply of products for developing countries.

Investment by the public and philanthropic sectors in lowering the costs and risks of vaccine development are among a group of instruments called 'push' interventions. These can take many forms including strengthening the 'system' capacities mentioned above (and more extensively in the main report), as well as support for testing different approaches to vaccine design.

Clearly commercial investment and skills will be recruited to vaccine development and supply if there is the prospect of a reasonable financial reward. A group of instruments that attempt to elicit commercial engagement in vaccine development by making the economic rewards more attractive are termed 'pull' interventions. Some 'pull' interventions increase revenues indirectly, for example strengthening health systems to increase coverage and hence the volume of product likely to be purchased.

Instruments for accelerating the development and introduction of vaccines needed in developing countries need to overcome (at least) two types of historical problem on commercial decision making:

- Low interest of commercial vaccine developers – both biotechs and bigger companies -- in engagement on products needed predominantly in developing countries; and
- Conservative sizing of manufacturing plant for new products, forgoing possible economies of scale, so that potential supply to developing country markets was limited and higher price, further contributing to slow adoption.

Vaccine companies think in terms of the revenues that particular products generate and thus discussion of buying potential products more predictably at prices better reflecting their public health value engages their attention. However, those 'pull' interventions that aim to provide a surrogate for a traditional market are but one element in the array of things that influence commercial decisions on whether and when in the development process to engage. Other important factors are where the envisaged products sit in the design and development progression, and the time to market/revenues compared to other products they or their competitors could pursue.

Alone, those 'pull' instruments that only provide a reward after vaccine licensure, do not share the costs of the many attempts at vaccine design by early risk-takers, that individually are likely to fail but which are essential for gaining the information on which the design of more effective products – and that of the ultimately successful product – will rest. Here the research institutes and biotechs are important players – both for innovative ideas and statistically – as typically the major vaccine companies, of which there are very few, only actively pursue their one most promising candidate at a time.

When candidate products need to be designed, made through pilot/production process development, and tested through collaboration among a range of actors in different institutions (rather than within a large vaccine company) there is a need for a coordinating body to move the candidate(s) through the steps outlined in Figure 1. This need is increasingly being filled by the product development partnerships (PDPs) like the Aeras Global Tuberculosis Vaccine Foundation, International AIDS Vaccine Initiative, the Malaria Vaccine Initiative and the European Malaria Vaccine Initiative. These ventures can manage a portfolio of candidate products and are well placed to do comparisons, dropping investment in the less promising candidates and replacing them in the portfolio with new designs based on accumulating information. They have been supported by philanthropic foundations (particularly the Gates Foundation) and by a small number of bilateral aid agencies, but most face significant funding shortfalls in the next few years.

Advanced purchase commitments (APCs) can take a variety of different forms:

'Inferred' advanced purchase commitments, arising from a predictable pattern of product purchasing behavior.

If the pattern of purchasing behavior is sufficiently predictable – and profitable – then the 'inferred' advance purchase commitment can motivate companies to invest in product development if other factors are favorable, e.g., the product is scientifically feasible. An 'inferred' advanced purchase commitment operates in industrialized countries to encourage vaccine manufacturing and vaccine development.

However, for twenty years historical patterns of international procurement for poorer developing countries have been highly price-sensitive (i.e., oriented towards the lowest price), relatively inaccurate in demand estimation, unpredictable on actual volume purchased, and short-term with usually annual off-take. To increase interest in supplying existing and new vaccines for developing country markets, significant changes and possibly new procurement actors/expertise may be necessary. This is also true of the two other types of advance procurement commitments described immediately below.

New funds (from the Gates Foundation, Canada, Norway, and the UK) to the Global Alliance for Vaccines and Immunization (GAVI) through the Vaccine Fund (VF) and the proposed International Finance Facility for Immunization, promoted by the UK should generate the development of more confidence on the part of vaccine producers in markets for existing vaccines. However, the best arrangements for implementing purchase commitments and otherwise building trust need to be identified.

Long term supply contracts for existing products provide some predictability for manufacturers and if awards are split among suppliers price competition and security of supply can be maintained. These have been discussed periodically but to the knowledge of the author not instituted by UNICEF until 2004 because funds provided to procurement agents have been until very recently only in annual installments.

APCs as a component of public-private planning for introduction of new products, could build confidence of vaccine developers/manufacturers of a future market. It can also yield mutual benefits, such as more predictable uptake/demand scenarios, assured supply capacity and better prices. Some steps towards such accelerated development and introduction plans (ADIPS) have been taken with rotavirus and pneumococcal vaccines, and are planned for Hib. These vaccines are licensed by major vaccine companies based largely in industrialized countries.

Another approach to planning the introduction of late stage products has been adopted by the Meningitis Vaccine Project of PATH which is targeting a conjugated polysaccharide vaccine against *N. meningitidis* type A, mainly for the meningitis belt in Africa. Under this approach there have been negotiations with a developing country manufacturer to be the 'recipient' of a new conjugation technology in return for an understanding on the future price of the product being low enough for the target countries to sustain.

While the processes of different sectors learning how to collaborate efficiently, estimate demand and uptake, and establish optimal procedures, e.g., on sole-suppliers while fostering future competition, are still in their early stages there are some clear practical opportunities to learn how advanced purchase commitments might be formulated for mutual benefit. These are described under 'Conclusions and recommendations'.

'Advanced Market'-type mechanisms, as proposed by the authors at the Center for Global Development, Washington, DC, USA. Under this approach an 'offer' is made by potential purchasers (sponsors) to pay a set price per course of vaccination for a product (or a succession of improving products) if it/they meets certain specifications, up to a limit. This type of proposal has received some general support as sending a desirable signal on the importance attached to HIV and malaria vaccines. However, a range of concerns, as yet unresolved, have been raised on the practicality of the Advanced Market-type of proposal. These mainly fall into the following categories:

- Questions and disagreements on the correct concept/model for early vaccine innovation;
- Doubts on its claimed utility in changing commercial decisions on whether to engage, especially heavily in early stages where uncertainties are greatest;
- Feasibility of implementation;
- Economic assumptions and modelling;
- Potential negative consequences;
- Appropriateness, given:
 - The potential for distracting attention from other, potentially more useful, interventions addressing the specific challenges and key actors at the early design stage where development of future HIV and malaria vaccines is currently located; and

- The potential for distracting attention from other urgent vaccination/vaccine development needs that could provide benefits earlier.

Current key players in HIV and malaria vaccine development

Noteworthy among current players are:

- Research institutes involved in translating concepts for vaccines into candidate Products, i.e., vaccine prototype design;
- Small biotechs, mostly but not only in industrialized countries, often working with PDPs; and
- Larger commercial R&D based vaccine companies, working sometimes on their own but also often with research institutes or small biotechs, and with PDPs.

The first two categories will collectively be a major factor in developing information that is critical to eventual success in development of HIV, malaria, and other vaccines, even if final licensure is by major vaccine companies. The first two types of organization mostly need 'pay-as-you-go' support for their involvement.

Other aspects of the overall vaccine development and introduction system need considerable strengthening to play their essential parts. In particular these include: expertise for production process development/manufacturing; capacities in disease endemic countries for disease burden studies, clinical trials and regulatory assessment'; clearer procedures for formulation of policy guidance; and expertise for demand assessment and in complex procurement arrangements.

Funding sources

The following conclusions are based on the information that could be gathered in the study period and should be updated based on other data gathering known to be currently underway.

Of overall funding for HIV vaccine R&D in 2004 from public and philanthropic sources (approximately US\$ 608 million), the USA provided 86.5% versus 8.3% from Europe. The main US source for funding HIV vaccine R&D is the NIH/NIAID which provides a broad array of mechanisms.²

Among developing countries Brazil, China, India, the Republic of South Africa (through the South African AIDS Vaccine Initiative, SAAVI) and Thailand are providing support for HIV vaccine development.

The recent consultation group for the Global HIV Vaccine Enterprise has recommended that support for HIV vaccine R&D be roughly doubled to US\$ 1.2 billion annually.

Of estimated (known) funding for malaria vaccine R&D in 2003 from public and philanthropic sources ((approximately US\$ 65 million), the USA provided roughly 88% versus around 12% from Europe. One estimate places the total expenditures on malaria vaccines for 2004 at US\$ 84 million.³

Thus funding for malaria vaccine R&D is around 15% of that for HIV vaccine R&D.

Even though information on funding sources gathered in this brief study is incomplete, missing data is unlikely to shift the picture significantly, as all major sources are probably captured.

² <http://www.niaid.nih.gov/daisd/vaccine/funding.htm>

³ Hoffman, S. 2004. Save the children: Creating a malaria vaccine will be tough. Nature 430: 940-941

Given the relative size of their aggregate economies, overall funding of HIV and malaria vaccine R&D by European and other industrialized countries appears to be at disproportionately low levels compared to that from the USA. This issue should be examined in more detail when country-specific figures are available.

Conclusions and recommendations

The charge for this study was to survey the development and introduction of vaccines into developing countries, including future vaccines against HIV and malaria, and to highlight the implications of that survey for those considering advanced purchase commitments.

Situation overview

The situation can be characterised as follows:

- A wide range of opportunities exist to save lives in developing countries through the use of existing vaccines (many of which are not being fully utilized) or the development of new vaccines, candidates for which are at various stages;
- A wide range of possible interventions, including different sorts of 'system strengthening', exist that could – with varying degrees of certainty – accelerate the development and introduction/utilization of vaccines in developing countries. These include advanced purchase commitments (APCs);
- One specific type of advanced purchase commitment (termed an Advanced Market-type approach) has been promoted in recent months as a means of accelerating development of HIV or malaria vaccines, which are essentially in the design/early development-stage;
- A wide variety of concerns have been raised regarding proposals for the Advanced Market-type APCs and many of these need further study, as the concept of 'due diligence' would require of potential sponsors of any APC;
- Beside the AM-type APC there exist a variety of other approaches to advance purchase commitments which would probably be easier to implement with existing or late development-stage vaccines because there is much greater certainty surrounding the products to which they could be applied;
- Advanced purchase commitments would ideally overcome two problems with commercial engagement in vaccines for developing countries: firstly, reluctance to engage in new product development specifically for developing countries; and secondly, conservative sizing of manufacturing capacity which occurs when a product is developed initially for more affluent markets, but which means that early supply and price for poorer developing countries are constraints;
- Measures to build confidence among commercial players in future revenues from vaccines (and hopefully increase their engagement in development/supply of vaccines for developing countries) would have greatest credibility if they start with the products that already exist;
- Public sector capacities in vaccine demand/uptake projection and procurement practices are historically regarded as unreliable, not subject to performance comparisons, and generally in need of strengthening and reshaping;
- GAVI and the Vaccine Fund have received pledges of increased funding that could be used for long-term supply contracts for existing products and infrastructure strengthening but total funding is still below the desirable level. The International Finance Facility for Immunization is urgently needed;
- For certain categories of recent products that are already proven to be capable of reducing disease burdens in developing countries (rotavirus, pneumococcal, and new combination vaccines), there will exist over the next few years a narrow window-of-opportunity to test (in a competitive environment) whether advance purchase commitments can influence manufacturers supply capacity and pricing decisions;

- Buying recent products at reasonable prices will not only increase vaccine producers confidence in future markets but will provide immediate revenues from which they can fund more R&D;
- A mix of different interventions *at each stage*, tailored to the different phases of vaccine development and introduction, will be needed to move the relevant candidates/products through the progression in an optimal manner. Support for overall 'system strengthening' is also essential;
- The specific utility of different forms of advanced purchase commitments and the priority for other forms of interventions and support needs to be examined in this context.

Advanced purchase commitments

As of the time of writing it is clear that a variety of types of advanced purchase commitment exist and further work is necessary to define which are most appropriate for different categories of vaccine. Included in this bigger picture is the need to resolve concerns around the Center for Global Development proposal for the Advanced Markets-type of approach to advanced purchase commitments for early stage vaccines.

It should be recognised that most of those who have raised concerns on the Advanced Markets idea do not question the usefulness of demonstrating a market 'pull' to engage industry, or the likely feasibility of advanced purchase commitments for existing or even late stage products. Their concerns are largely whether an experimental mechanism such as the Advanced Markets proposal is feasible, appropriate for early stage vaccines where there is great uncertainty as to the likely product, and likely to have the desired impact on decisions.

It is **recommended** that an impartial 'blue-ribbon' panel of economists, experts in vaccine development, and commercial pharmaceutical investors should be charged with recommending, within six months, how to proceed on the range of possibilities for advanced purchase commitments, and other activities to accelerate vaccine development and introduction for developing countries.

Key questions the group should examine include:

- What forms of advanced purchase commitments are potentially useful and feasible in engaging commercial vaccine development resources on products for developing countries and in what form for vaccines at different stages of development?
- What other instruments and forms of support should be given priority, taking into account the development-stage of important vaccines for developing countries and the needs to strengthen the overall vaccine development and introduction system?
- Where advanced purchase commitments are potentially most useful in encouraging appropriate sizing of manufacturing plant capacity to meet rapid introduction needs in developing countries?

As described below there are, in fact, a number of ways in which credible 'pull' or advanced purchase commitments could be explored to address immediate needs and gain experience.

Among those that should be brought to the attention of the panel is that over the next 0-4 years developers of rotavirus, pneumococcal and new combination vaccines currently licensed or about to be submitted for licensure may be making decisions on new or expanded production capacity. This represents an immediate but narrow 'window of opportunity' to see if advanced purchase commitments can in fact influence commercial decision-making on sizing of production plant, which as noted above is one of the key problems that APCs need to overcome to expedite disease control in developing countries.

Matching instrument and financial support to product development stage, system strengthening needs and other opportunities to use vaccination to address diseases associated with poverty

Juxtaposing the various categories of vaccines (early development stage, late development stage, 'recent', 'underused') against the steps in the vaccine development and introduction process (Figure S.1.) suggests that different interventions (or more likely **a mix of different interventions**) will be needed **at each stage** to move the relevant candidates through the progression in an optimal manner. These will probably include:

- 'Push' interventions, to accelerate candidate product design/development by engaging many players;
- 'Pull' interventions, that variously provide economic reward and assure product use, both directly through purchase and indirectly by establishing the delivery systems that mean products can reach maximum number of recipients;
- Product development partnerships, i.e., brokers to expedite the passage of candidate products down the development and introduction pathway, as this needs many linkages; and
- Support for system strengthening as a whole (as described in the Background section, C.1.).

This conclusion is reinforced if one considers the wider 'system' capacities that are needed. Financial reward should be assured for commercial players but even significant rewards would not overcome the problems and delays that are caused by lack of capacities that only the public sector could or should provide, such as regulatory assessment or comparative testing.

The conclusion is further reinforced by the fact that future vaccine development and supply for developing countries may not be solely a function of the activity of the traditional major companies but is likely to involve a greater role by new players such as applied research institutes, not-for profit product development partnerships, biotechs, and developing country manufacturers. These will require cost sharing on a pay-as you-go basis as they cannot generally mobilise major resources from revenues on other products as can large pharmaceutical companies.

Table S.1 shows the present and future opportunities for alleviating diseases associated with poverty through vaccination, i.e., both by applying existing vaccines and accelerating the development and introduction of new vaccines. It suggests a strategy to consider advance purchase commitments for HIV and malaria vaccines based on the experience that will come from developing advanced purchase commitments successively for: (i) existing under-used vaccines; (ii) 'recent' new vaccines; (iii) late development stage vaccines; and ultimately (iv) early development stage vaccines (if judged feasible and useful).

It is **recommended** that any pledge to develop advanced purchase commitments for a range of existing and future products should be accompanied by agreement to rapidly establish priorities for the other 'push' and 'system strengthening' interventions that need to be in place, through the 'blue ribbon panel' discussed above.

A comprehensive approach will give confidence to all the necessary players, including major commercial companies, that the commitment to vaccination against the diseases associated with poverty is broad and will last long beyond the upcoming G7/8 round.

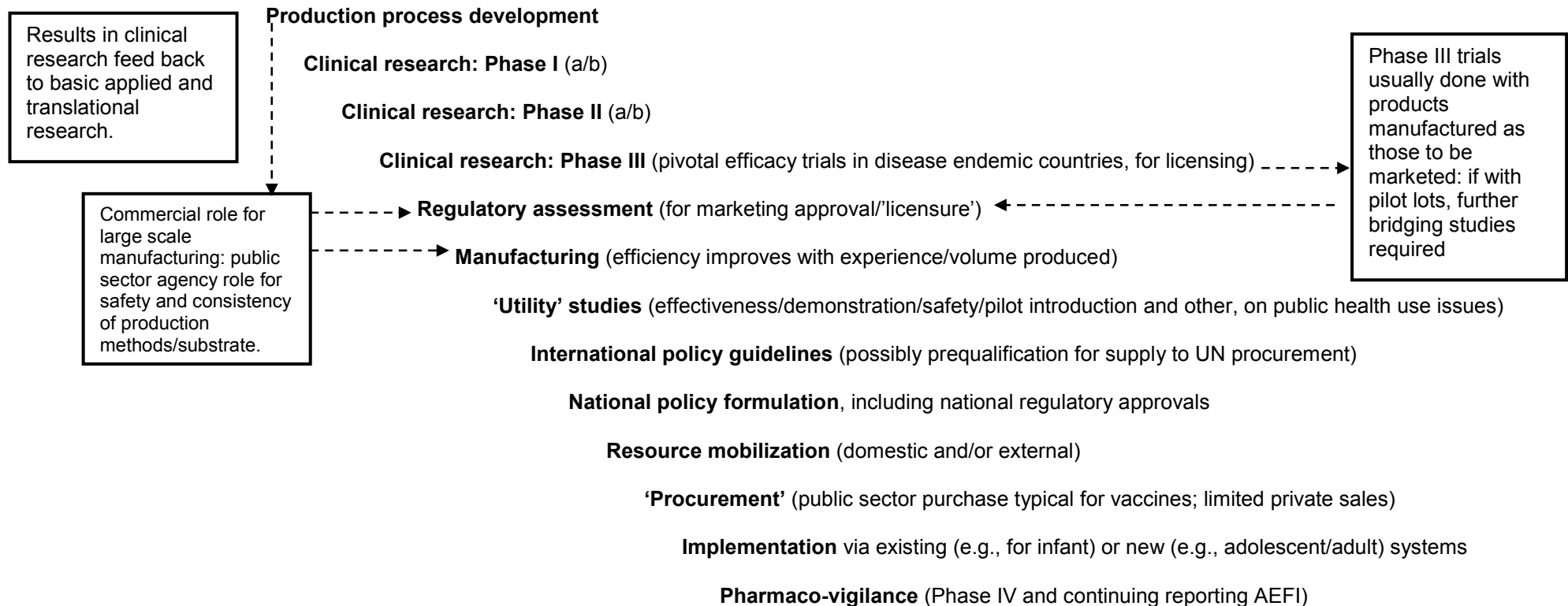
Figure S.1: Steps in vaccine development and introduction into poorer countries

Basic research (for understanding of pathogen, host response, epidemiology)

Applied research (yields concepts/targets for vaccine design)

Translational research⁴ (translates concepts into candidate products/initiates process development/pilot lots)

Preclinical research (tests concepts/designs in animal models, if available)



⁴ This report uses the term 'Translational research' as defined here, although it is sometimes applied to what in this schema are called 'Utility studies'.

**Table S.1: Accelerating vaccination for control of diseases associated with poverty:
Location of major challenges and current needs**

Vaccine category	Disease/vaccine examples	Vaccine design or development issues	Use policy issues	Supply/procurement/ issues	Delivery system issues	Current major needs		Comments
						Candidate product related	'System' related	
Under-used	DTP Measles Hepatitis B Rubella	None	None (except for Rubella strategy safety)	Adequate, competitive global supply capacity exists	Lower reach (sometimes <50%) to poorest/rural infants in developing countries	Adequate funding for multi-year supply contracts, split among low cost suppliers to maintain competition	Better demand estimates Funding to strengthen delivery 'infrastructure' and other DEC capacities e.g., for trials and regulation	Polio eradication should be completed. Complete implementation in 0-5 years
'Recent'	Hib New combinations e.g., DTP+, others Rotavirus Pneumococcal	None (competition anticipated where currently sole suppliers)	For some vaccines disease burden studies and cost-effectiveness analysis needed	Production technologies well known: supply capacity likely to be adequate if market demonstrated	Lower reach (sometimes <50%) to poorest/rural infants in developing countries	Funding for multi-year supply contracts, split among lower cost suppliers to encourage competition Policy guidelines for newest	As above. Policy for higher prices for initial purchase for poorer countries to encourage new scale manufacturing Learning from APCs for 'under-used' vaccines	Over next 0-10 years
Late development stage	Meningococcal A Alternative pneumococcal HPV New combinations	Design issues mostly known Pneumococcal options desirable (easier production, cheaper), if feasible	Mostly known	Production technologies known and can be scaled for sufficient supply	As above	'Push' support to clinical trials Support to PDPs and ADIPs Anticipation of required utility studies for policy formulation	As above Projections of uptake/demand Learning from APCs for 'recent' vaccines	Over next 0-15 years

(Continued)

**Table S.1: Accelerating vaccination for control of diseases associated with poverty:
Location of major challenges and current needs**

Vaccine category	Disease/vaccine examples	Vaccine design or development issues	Use policy issues	Supply/procurement/ issues	Delivery system issues	Current major needs		Comments
						Candidate product related	'System' related	
Early development or 'design' stage	HIV/AIDS Malaria Tuberculosis Leishmaniasis	Information needed to design more effective candidate products, but difficult/costly to generate	Mostly difficult to anticipate absent knowledge of vaccine design; some difficult safety and strategy questions already identified	Difficult to foresee, beyond those historically known for existing or late stage products	As above. For HIV vaccines: delivery system to adolescents/adults in poorer countries needs creating	Support to applied research; translational research; pilot lot production; assays, standards, definition of trial end-points etc for comparisons. Support to PDPs and other 'Push' Instruments	As above Learning from APCs for under-used, recent and late stage vaccines	Some actions needed now but timeframe for completion uncertain

Key Stakeholders and Funding of HIV and Malaria Vaccines: Considerations in selecting appropriate instruments for accelerating public health impact of vaccination in poorer countries

Abbreviations

ABL	Advanced Bio Sciences Laboratories
ACTs	Artemisinin Containing Therapies
ADIPs	accelerated development and introduction plans
APCs	advanced purchase commitments
APCO	Affaires Publiques et Communication Stratégique, France
AM	Advanced Markets
AMD	Alliance for Microbicide Development
ANRS	Agence National pour Recherche sur SIDA
AVAC	AIDS Vaccine Action Coalition
CDC	Center for Disease Control
CGD	Center for Global Development, Washington, DC, USA
DECs	disease endemic countries
DFID	Department of International Development, UK
DOD	Department of Defense, USA
DTP	Diphtheria, tetanus and pertussis vaccine
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration, USA
GAVI	Global Alliance for Vaccines and Immunization
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GSK	GlaxoSmithKline
GSK BIO	GlaxoSmithKline Biologicals, Belgium
IAVI	International AIDS Vaccine Initiative
IDT	Impfstoffwerk Dessau – Tomau GmbH
IFF	International Finance Facility
IFFI	International Finance Facility immunization
MMV	Medicines for Malaria Venture
MRC	Medical Research Council
NIAID	National Institute for Allergy and Infectious Diseases, NIH, USA
NIH	National Institute of Health
NMRC	Naval Medical Research Center, DOD, USA
NRA	national regulatory agency
PATH	Program for Appropriate Technology
PDPs	Product development partnerships
PPP	Public-private partnership
SAAVI	South African AIDS Vaccine Initiative
SII	Serum Institute of India
STI	Swiss Tropical Institute
UMMS	University of Massachusetts Medical School
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WHO CIPIH	WHO Commission on Intellectual Property, Innovation and Health
WRAIR	Walter Reed Army Institute of Research

Key Stakeholders and Funding of HIV and Malaria Vaccines: Considerations in selecting appropriate instruments for accelerating the public health impact of vaccination in poorer countries

A. Introduction

This paper aims to provide a broad context within which possible advance purchase commitments (APCs) and other interventions to accelerate development and introduction of vaccines for developing countries, including those for HIV and malaria, can be evaluated.

A range of other studies relevant to the topic under consideration were underway at the time of writing: these are identified in Section B.

Section C of the paper lays out the steps for vaccine development and introduction into poorer countries. This should enable readers to place the main current and future challenges to HIV and malaria vaccine development and use in a broader context and appropriate timeframe. Advanced purchase commitments target commercial players so this background section includes an overview of the recent trends and markets for pharmaceuticals, vaccines overall, and vaccines for developing countries. It also includes a short discussion of the factors thought to influence commercial decisions on development of pharmaceutical products including vaccines.

Section D of the document is structured according to the principal components of the Terms of Reference (Annex 1):

- Players in R&D for HIV and malaria vaccines;
- Funding sources for HIV and malaria vaccine R&D;
- Strengths and weaknesses of the overall system for vaccine development and introduction;
- Instruments for accelerating vaccine development and introduction;
- Implications for advance purchase commitments and other instruments.

Finally, conclusions and recommendations are presented in Section E.

B. Scope of study and other assessments currently underway

This report derives from a project of limited duration undertaken on a short deadline. Consequently, it could not cover all of the aspects of the Terms of Reference in great depth. Details in some areas such as the levels of national funding for HIV and malaria vaccine development would have required a more extensive project to cover in the desirable level of detail.

Readers should bear in mind that a number of related studies are underway that will provide more detailed information on certain aspects of the charge.

These include:

Global Funding for Malaria Research and Development by APCO Worldwide and the Chartis Group; commissioned by the Malaria Vaccine Initiative at PATH, for completion in August 2005.

Public, Philanthropic and Private Sector Investments in Preventive HIV Vaccines and Microbicides: 2000-2004, by the HIV Vaccines and Microbicides Resources Tracking Group (AVAC/AMD/IAVI/UNAIDS), for completion in May 2005.

Global Vaccine Supply: the Changing Role of Suppliers by the Boston Consulting Group, USA, for the Global Alliance for Vaccine and Immunization and World Bank, for completion July/August 2005.

Socio-Economic and Financial Evaluation of the Medicines for Malaria Venture (MMV) Portfolio for the Bill & Melinda Gates Foundation and MMV. (Although on drug development economics, this study is relevant to industry interest in developing products for 'neglected diseases' of poorer populations.) The management consulting group to undertake the study is to be selected in April and completion is expected in the late summer of 2005.

Report of the WHO Commission on Intellectual Property, Innovation and Health, World Health Organization, completion expected in late 2005.

It is recommended the reports from these studies be reviewed when available, to determine the extent, if any, they would modify the conclusions in the document.

C. Background

C.1. Overview of the necessary steps in vaccine development and introduction into use in developing countries

The steps necessary for development and introduction of vaccines into use in developing countries, are shown generally in Figure 1.

Focussing on the passage of candidate products through the development and introduction steps, or ways to accelerate this, entails the danger that the 'system' as a whole may get ignored. Sponsors of candidate products rely on a wide range of other capacities to be in place. If supportive capacities are absent or deficient, the system as a whole functions inefficiently with unnecessary delays. Many of these supportive capacities are functions that it is not appropriate for commercial companies to pay for (e.g., regulatory oversight or formulation of international guidelines for use) or things the public sector has responsibility to pay for. The latter category includes clinical research training and trials capacity in developing countries, disease burden studies and effective procurement systems).

This paper takes the view that support and incentives for product development and introduction need to be accompanied by investment to optimize the overall 'system' for these activities. Only with a balanced approach to both will the ultimate objective – reducing morbidity and mortality – be obtained quickly and cost-effectively. It is also desirable to address issues in introduction of vaccines into developing countries early as historically this has been subject to unnecessary delays. These have arisen variously from poor disease burden estimates (Hib), failure to plan for financing (HB), failure to project demand (combinations), and failure to address strategy safety issues (rubella).

Accelerating the development of vaccines that will most likely be primarily used for the control of diseases associated with poverty, has no real precedents.

Instruments specifically aiming to motivate commercial engagement in development and introduction of vaccines needed in developing countries need to overcome (at least) two types of historical problems:

- Low interest of commercial vaccine developers – both biotechs and bigger companies – in engagement on products needed predominantly in developing countries; and
- Conservative sizing of manufacturing plant for new products, forgoing economies of scale, so that potential supply to developing country markets was limited and high price, further contributing to slow adoption.

For the last 50 years, vaccines have typically been developed and initially manufactured by large commercial pharmaceutical companies to meet perceived public health needs in affluent populations. These vaccines then 'trickled down', with considerable delays, to wide application in poor countries, where the same diseases also occur. Developing country use depended at least initially on experience and capacities in affluent countries (e.g., regulatory approval systems, and pharmaco-vigilance (for safety in broader use). Studies were sometimes needed for adapting products to developing country use (e.g., for oral polio vaccines) as well as studies to verify the assumed disease burdens (e.g., for Hib disease).

The historical 'system' through which vaccines are developed is itself in a process of change. Scientific advances have created the knowledge and tools to explore more and different approaches to vaccine design. This has fueled the creation of a plethora of small (and nowadays not so small) 'biotech' companies to test new approaches. These expand and replace work previously conducted on a much smaller scale in academia. Financial sector organizations, where they see future profit have brought new funding, not tied to vaccine sales

revenues, to these 'biotechs'. This 'venture capital' has more recently been matched by substantial funding – sometimes termed 'social venture capital'-- from philanthropy and public sector aid agencies for not-for-profit product development for diseases associated with poverty. The major commercial companies engaged in vaccine development are pursuing their work in different ways. At the early stages of development, many are relying more on a portfolio of commercial links to 'small biotechs' to identify the most promising candidates, and less on picking potential winners from early development activities conducted in-house.

Prospects for more rapid utilization of new vaccine in the poorest countries have been boosted recently by new players and new mechanisms. The Children's Vaccine Initiative (1990 - 1999) highlighted the growing gap between vaccines utilized in affluent and poor countries and identified steps needed to reverse this trend. The Global Alliance for Vaccines and Immunization and its companion Vaccine Fund were created in 2000 as successors to the CVI, primarily to address the earlier introduction of new vaccines to poorer countries and the infrastructure to support this. Substantial funding from the Bill & Melinda Gates Foundation and a few bilateral aid agencies (e.g., Canada, Norway, UK, and USA) has made this feasible.

A range of not-for-profit ventures were created from the mid-1990s into the early 2000s to address accelerated development of vaccines for diseases associated predominantly with poverty (e.g., the Aeras Global Tuberculosis Vaccine Foundation, EMVI, IAVI, MVI, the Human Hookworm Vaccine Initiative and the Pediatric Dengue Vaccine Initiative).⁵

GAVI also came to serve as an 'umbrella' for accelerated development and introduction plans (ADIPs) for new vaccines now emerging from commercial companies to combat rotavirus diarrhea and pneumococcal pneumonia. Another ADIP will soon address Hib vaccine, the uptake of which has been slower than initially expected.

More recently the global development community created the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). This is not engaged in funding product-related R&D. However, because it is funding procurement of new health products, for example Artemisinin Containing Therapies (ACTs) and impregnated bed nets, it might also be important in the future as a resource for new vaccine procurement. The GFATM is largely funded by affluent countries particularly via their development assistance agencies.

Even more recently proposals for an overall International Finance Facility (IFF) and one specifically for immunization (IFFI) have signalled positively, if in general terms, on the prospect for revenues from products to control specific diseases of the developing world.

⁵ See Widdus, R. and White, K. 2004. Combating diseases associated with poverty: Financing strategies for product development and the potential role of public-private partnerships. Initiative in Public-Private Partnerships for Health, Geneva, 214pp.

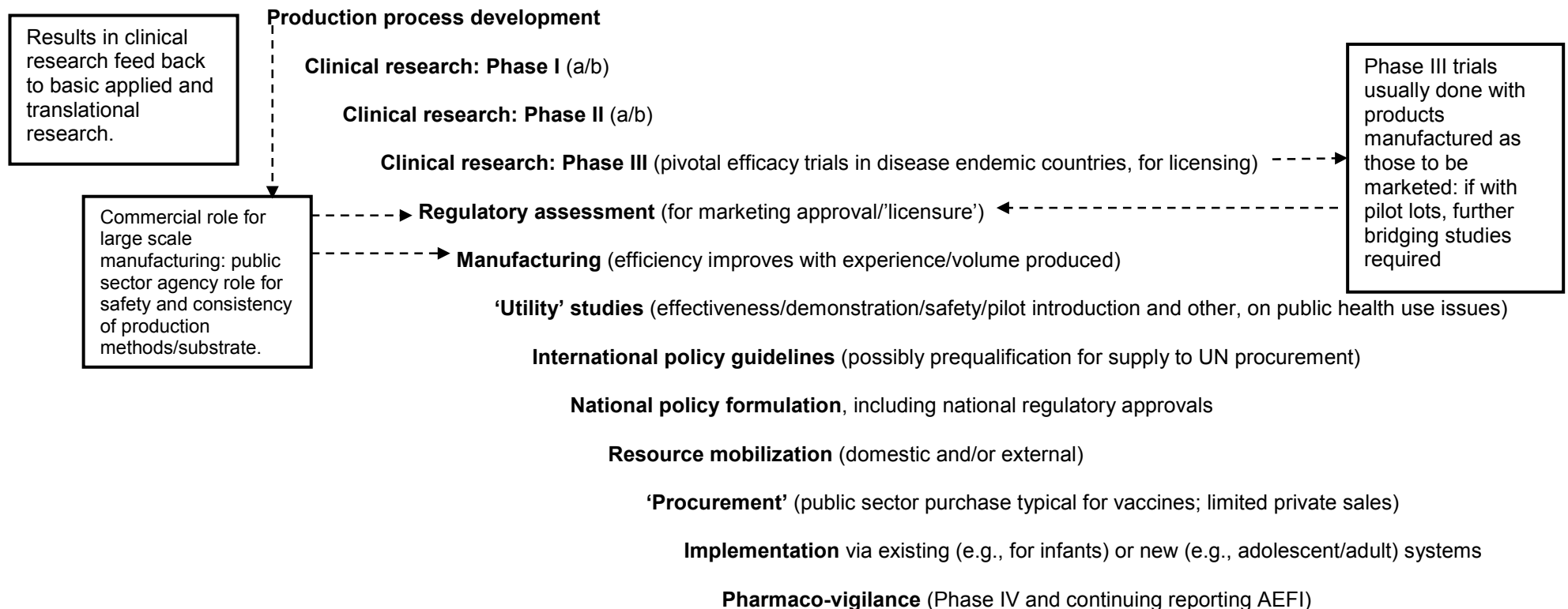
Figure 1. Steps in the development and introduction of vaccines into poorer countries

Basic research (for understanding of pathogen, host response, epidemiology)

Applied research (yields concepts/targets for vaccine design)

Translational research (translates concepts into candidate products/initiates production process development/pilot lots)

Preclinical research (tests concepts/designs in animal models, if available)



This report uses the term 'Translational research' as defined here, although it is sometimes applied to what in this schema are called 'Utility studies'.

C.2. Global and developing country markets for pharmaceuticals and vaccines

Preventive vaccines are a component of the market for 'bio-pharmaceuticals'⁶, which in turn, is part of the bigger pharmaceuticals market.

Most recent new vaccines have been put through at least the latter stages of development and brought to market by large R&D-based vaccine producers which are typically part of larger commercial pharmaceutical companies. Such companies have to be concerned with profits on existing products and the likelihood that investments in R&D will result in products that have a high probability of contributing to a future healthy revenue flow, preferably sooner rather than later.⁷

The global pharmaceutical market has been growing substantially in recent years, predominantly driven by sales in industrialized countries particularly the United States of America.

For 2004, the global pharmaceutical market is estimated at US\$ 550 billion.⁸ At the time of writing no precise figures on the 2004 global vaccine market were available but based on previous years, it is believed to be in the range of US\$ 6.5 billion to 7.0 billion, or around 1.5% of the total pharmaceuticals market.

Reliable time series data on the fraction of the global pharmaceuticals market that vaccines comprise could not be located during the course of this short study. However, it seems to the author from anecdotal information over the last two decades that while growing in absolute terms, particularly in industrialized countries, the vaccine market has probably been shrinking as a fraction of the global pharmaceuticals market.

This is probably because generally vaccines are commercially unattractive compared to drugs.

- Vaccine development historically has required major investment in product-specific manufacturing plant (for clinical trials) before the certainty of a marketable product (and revenues) is established.⁹ (Drug manufacturing on the other hand can be scaled up after efficacy is established).
- Purchasers of vaccines (generally governments) are typically quite price-sensitive and, because of their monopsony (dominant purchaser) power, able to negotiate lower prices (hence lower margins) than patients seeking (drug-based) therapies.
- The target population for vaccines – healthy individuals – requires close to absolute safety and side-effects discovered post-marketing (e.g. Wyeth's rotavirus vaccine) can cause expensive product withdrawal.
- Alleged adverse reactions create undesirable reputational and legal claims risk for producers even if the allegations are scientifically unfounded. This is a greater problem for vaccines because they are administered to the vast majority of healthy infants/children at an age when health problems particularly neurological ones are starting to become apparent anyway.

Understandably, this situation leads to lower interest by major pharmaceutical companies in vaccine development in general and to even lower interest in vaccines with predominant demand in poorer populations. Most major vaccine companies now focus on a selected rather than a comprehensive range of candidates in development – and these are likely to be ones which clearly have affluent markets.

⁶ 'Bio-pharmaceuticals' also include therapeutic biological agents.

⁷ Return on investment (ROI) calculations are complex, not simply a matter of 'paying back' R&D costs, but also incorporate the cost of failures, time to market, and cost of capital, *inter alia*.

⁸ <http://www.imshealth.com/ims/portal/front/articleC/0.2777.6599.3665.71496463.00.html> accessed 30 March 2005

⁹ Mercer Management Consulting 1995, Report on the United States Vaccine Industry, for the Department of Health and Human Services. 33pp.

Particularly in the United States of America, there has been a general withdrawal from the vaccine manufacturing sector, starting around the mid-1970s when regulatory requirements started to increase significantly along with legal claims from alleged vaccine injury.

The ‘developing country’ vaccine market

Developing countries, particularly the least developed, are highly price-sensitive regarding pharmaceutical products because of their poverty. Bilateral aid donors, who provide resources for vaccine procurement and use in the least developed countries (directly and via UNICEF), likewise have traditionally wanted low vaccine prices.

In 2002, Mercer Management Consulting estimated that the global pharmaceutical market was US\$ 340 billion, global vaccines amounted to US\$ 6 billion, and vaccines to developing countries about US\$ 0.3 to 0.4 million.¹⁰ Mercer Management Consulting estimated that while ‘developing’ countries amount to about half of the global vaccine market by volume (doses) they account for only 5% of revenues, and this in the most part is for traditional vaccines on which suppliers from countries with low-production costs (but less innovation capacity) have an advantage. More recent and time series data could not be obtained in the duration of the project. Purchases by GAVI/ the Vaccine Fund may have increased the developing country market in recent years. However, the market for poorer countries has still tended to be high-volume, low-margin business with a limited number of procurement agents (mostly UNICEF for the poorest countries and PAHO for the Americas) and these tend to use their monopsony position to achieve low prices. That such business is unattractive for most industrialized country producers (that are the historical innovators) is illustrated by the fact that US manufacturers do not generally respond to UNICEF tenders, and the fraction of the UNICEF market taken by developing country or emerging economy manufacturers has risen as shown in Table 1.

Table 1. Purchase of vaccines by United Nations agencies

Year	Number of vaccines	Number of suppliers	% located in developing countries or emerging economies
1986	4	7	0
1996	5	14	50
2001	6	12	58

From Milstien J. and Widdus R. 2003 facilitating access to vaccines: An overview of legal and political issues. *Pharma. Dev. Regul.* 1 (2): 101-116.

This trend may have reversed slightly in the last couple of years, but only for new vaccines and combinations that developing country manufacturers have not yet mastered.

The author estimates that in 2004 the global pharmaceuticals market amounted to US\$ 550 billion (IMS data), the global market for vaccines about US\$ 7.0 billion at most (up from US\$ 6.0 billion in 2000, Mercer Management Consulting estimate) and the market for vaccines to the poorer developing countries as – at most – US\$ 0.5 billion (up from US\$ 220 million in 2002, UNICEF data). The largest selling individual vaccine (recently licensed Prevnar® for pneumococcal pneumonia) has estimated sales of over US\$ 1.0 billion, mostly in the USA. ‘Blockbuster’ drugs on the other hand can individually generate annual sales of US\$ 5.0 billion

¹⁰ Mercer Management Consulting, 2002 Lessons Learned, a study of vaccine procurement for GAVI.

or above and large pharmaceutical companies may nowadays be uninterested in products with sales less than US\$ 500 million (up from \$ 300 million in 1997 as estimated by Mercer Management Consulting).

In the period 1980 - 2000, the pharmaceutical and vaccine industries experienced a range of mergers and acquisitions. These continue, as do a range of collaborations between established global R&D-based suppliers based in industrialized countries and the developing country producers that are capable of high quality production. Examples include producers in Brazil, China, Indonesia, and Thailand, who see these arrangements as a way of accessing more rapidly new production technologies (e.g., for Hib vaccine) that usually they have mastered only slowly if at all.

Traditional, usually state-owned, national production facilities underwent major changes in the late 1990s. The situation in the early 1990s was reviewed in a document published by the Children's Vaccine Initiative in 1999.¹¹ From a much longer array in the early 1990s, a small group of producers has emerged as capable of manufacturing to internationally accepted quality. (See the website of the Developing Country Vaccine Manufacturers Network at www.dcvmn.org.) This is usually judged by a fully functioning national regulatory agency (NRA) and 'prequalification' by the World Health Organization for supply to UN agency procurement.

Certain private sector producers [e.g., Serum Institute of India Ltd. (SSI)] have continued to meet international standards. SSI has also started to collaborate with the Meningitis Vaccine Project at PATH, to acquire polysaccharide conjugation technology, initially for Meningitis A vaccine development, licensure and manufacture.

Historical vaccine producers in large or advanced countries, have been joined by a small, but growing group of new manufacturers of relatively new vaccines (e.g., for Hepatitis B). These 'biotech' producers (e.g., Bharat Biotechnology International Ltd. and Shanta Biotech Ltd) reflect the emergence of a small but growing biotech industry in advanced developing countries.

Current vaccine manufacturing capacities

The brief survey above of shifts in vaccine development and manufacturing over the last 25 years sets the scene for a general categorization of the current worldwide capacities in vaccine development and manufacturing. These can be loosely grouped as follows:

Based in industrialized countries:

- R&D-based innovator companies, global suppliers, large scale manufacturing experience, part of large pharma;
- R&D-based innovator companies, suppliers predominantly to industrialized countries, medium scale manufacturing, part of large pharma;
- Vaccine specialty companies, medium scale manufacturing, not part of large pharma.

Based in advanced or large developing countries, and emerging economies:

- Global suppliers, large scale manufacturing experience, fully commercial, limited R&D-capacity;
- Moderate to large scale suppliers predominantly to domestic markets; sometimes with quasi-governmental or favored-supplier status; some with emerging R&D capacity;
- Recently emerging vaccine specialty 'bio-tech' companies, generally small scale manufacturing, but with increasing innovation potential.

¹¹ Children's Vaccine Initiative, 1999, Local vaccine production: Issues of quality and viability, prepared by J. Milstien.

Until the mid-1990s vaccine manufacturing in developing countries was predominantly limited to traditional vaccines, and had limited capacity to master new technologies, or to innovate themselves for new products.

The situation is clearly changing but the speed of the change and the implications for global vaccine supply are not yet fully clear. Developing country manufacturers could play a significant part in making new products available to poorer markets since they can be lower cost manufacturers and – generally not being part of ‘big pharma’ – are willing to target lower margin market niches. It will be easier to assess this possibility after the completion of the GAVI/Boston Consulting Group study of ‘Global Vaccine Supply’ mentioned in Section B.

Biotech industry capacities for vaccine development and manufacturing

In the last few decades, many so-called ‘biotech’ companies have emerged, initially undertaking exploratory research and early product development in the health field. Their capacities in the USA, Europe, and advanced developing countries can be respectively described as extensive, growing and embryonic. A few such companies in the USA and Europe have brought products to market. However, it is reasonable to generalize that their contributions in the next decade or two will predominantly be in the early stages of new product development. Relatively few have extensive experience of large clinical efficacy trials in developing countries and few have manufacturing capacity.

These entities are funded in various ways: venture capital; private investment; government grants and contracts; and sometimes agreements with major pharmaceutical companies. Few have revenue streams from marketed products but many of them and their investors anticipate growing, manufacturing and marketing. Some may see being ‘bought out’ by large ‘pharma’ as the path for their candidate products, if successful, to pass through final development and licensure.

Whatever their anticipated path, it is necessary to emphasize the importance of these ‘biotech’ entities to applied research, design and early testing of new products for HIV, malaria, and a host of other new vaccines. These groups are taking on a major role in generating new knowledge for product design and development. They are likely collectively be a major factor in developing information that is critical to eventual success in development of the ultimate vaccines for HIV, malaria, and other diseases, even if final licensure is by major vaccine companies.

What drives commercial decisions in development of pharmaceuticals, including vaccines?

Company decisions on product development investment take into account a wide range of factors, in addition to the potential for revenue. The major ones are listed in Table 2.

Table 2: Factors in commercial company product development decisions.

- In-house expertise to conduct (or manage) the required development steps;
 - Availability of product leads or candidate products in which the company has a strong intellectual property position (patents, and/or know-how);
 - Likely revenue stream the envisaged market can provide, including likely market share;
 - Time to market;
 - Position of other candidate products in competitor pipelines;
 - Scientific feasibility, risks of failure;
 - Capacity to set “go/no-go” milestones, preferably early, to curtail development of costs of ‘failing’ products (e.g., before full scale production facilities);
 - Investments necessary to reach milestones, licensure, and full revenue;
 - Familiarity with environment for product testing;
 - Uncertainties in regulatory issues or pathways;
 - Familiarity with envisaged markets;
 - Difficult-to-resolve safety questions (which can add to cost via requirements for phase IV studies, and these can be expensive if pharmaco-vigilance systems need to be established to conduct the studies);
 - Reputational risk in product development (e.g., from ‘exploiting’ test subjects) or marketing;
 - Product or disease ‘champions’ in-house;
 - External expectations, e.g., of shareholders, and political leaders;
 - (To some degree) ‘fashion’ or what is perceived as a ‘hot topic’ or exciting/potential opportunity, such as genomics or bio-defense;
 - Other in house or negotiable product development opportunities for investments of resources, and their relative promise as judged by the factors as above.
-

A similar set of factors governs venture capital investor decisions on support for small ‘biotech’ companies.

Shifting one of these factors favorably for particular candidate product, e.g., potential revenues, through a promise of a market, will not necessarily affect the overall decision if the other factors are negative or uncertain compared to other available opportunities.

In 2000 the World Bank commissioned Mercer Management Consulting to undertake a study of commercial decision making on engagement in HIV vaccine development. The study, reported in 2001 by Batson and Ainsworth¹², illustrates the many issues that go into decision making for early stage vaccines.

¹² Batson, A. and Ainsworth, M. 2001 Private investment in AIDS vaccine development: obstacles and challenges. WHO Bulletin 79: 721-726.

C.3. Special features of vaccine development for HIV/AIDS and malaria

Development issues

The development of most vaccines in current use has largely rested on the observation that for particular diseases individuals who recover from infection display immunity that protects against re-infection with the same strain at least for some period. Where post-disease immunity is absent or poor, vaccine development has proven more difficult. In some case, the knowledge of the mechanism of naturally acquired immunity is very limited and vaccines have been developed 'empirically', but still based on the knowledge that some immunity from natural infection did occur.

In recent years there have been some examples of vaccine technology improving on naturally acquired immunity. The principal example in the capacity to generate at a younger age long-lasting immunity to polysaccharide antigens (such as those stimulating natural immunity to *S. pneumoniae*, *Haemophilus influenzae* type b [Hib]; and *N. meningitidis* in children over two years old) by conjugating them to protein carriers. This approach was based on a reasonable knowledge of the immune system responses of younger children to protein and polysaccharides. However, other examples of improving on natural immunity are rare.

In the case of HIV/AIDS, the virus eventually breaks down the host immune system and (as far as the author is aware) there are no well-documented cases of recovery from established infection.

Vaccine design development is facilitated when animal models mimicing the human infection/disease are available. These are most useful where the process of infection, disease and response/recovery are close in all respects to the human pattern.

Primate models exist for HIV-1 infection in humans and some offer suggestions that a vaccine for humans may be possible. Certain of these may offer some help in vaccine design and identifying correlates of immunity. However there will need to be careful validation in humans of any suggestions emerging from these animal models as none of the models closely matches infection and disease in humans. No clear correlates of protection are known although it is assumed that both antibody and cell-mediated immune responses will be needed. Knowing what to put in the vaccine to get the required protective responses – vaccine design – remains the critically important step on which further vaccine development and subsequent improvement will rest. (See Global Vaccine Enterprise Scientific Plan).

Hence, vaccine design and development against HIV is difficult. How to design vaccines that **improve** on the poor natural protection from infection and disease will not be easily elucidated from studies of natural pathogenesis. Rather knowledge on how to manipulate the immune system to provide better protection than nature are likely to come from intervention approaches in large human population trials. Each of these is expensive, and, realistically most of the early 'experiments' are not likely to yield a highly effective vaccine. The state of scientific knowledge thus determines the most expeditious way to proceed.

In the case of malaria, older children and adults do acquire partial clinical immunity – showing lower morbidity and mortality – from repeated exposure. However, to protect infants and malaria-naïve adults, vaccine development again must improve on naturally occurring immunity.

Various factors complicate malaria vaccine development.^{13 14} These include: the fact that there

¹³ Richie, T.L. and Saul, A. 2002. Progress and challenges for malaria vaccines. *Nature* 415:694-701.

¹⁴ Hoffman, S. 2004. Save the Children: Creating a malaria vaccine will be tough. *Nature* 430:940-941.

are different species and strains of the parasite(s) causing malaria; the multi-stage life cycle of the parasite(s); the fact that the different stages display numerous antigens many of which seem to be involved in the limited natural immunity that exists but to unknown degrees; and the variety of human responses to different antigens. In the 1970s it was shown that animals and human volunteers immunized with irradiated sporozoites (the agent transferred by mosquitoes) acquire immunity but this wanes after some months. This suggested the possibility of a vaccine but unfortunately, this approach (at least until recently) has not been considered amenable to large scale vaccine production.

Most development of candidate malaria vaccines has focused on one or a few specific antigens connected with single stages of the parasite life cycle. Only one *P.falciparum* protein has been significantly evaluated in early clinical trials and the lead candidate based on this has been jointly developed between GSK with the US Army (through WRAIR). It first went into clinical testing in 1986. Results from Phase IIb trials of this candidate in 2000 children in Mozambique supported MVI were released in late 2004. It show promise for severe disease and larger Phase III trials are planned. Even if these prove successful – which is not certain – it will likely be regarded as a first generation vaccine that will almost certainly require successive improvements. A range of other antigens, for different stages, and different strategies (e.g., ‘prime-boost’) are being pursued but are at earlier design/early-development stages of testing than the GSK/WRAIR lead candidate. There is a clear consensus that while the current GSK/WRAIR is promising it would be a mistake to slow development of other possibly more effective candidates.

Many commentators believe the most effective malaria vaccines will ultimately be multivalent, i.e., targeting all the different stages of the parasite life cycle and doing so with a range of antigens related to each of the different stages. (See footnote to Richie and Saul, 2002, on previous page). With malaria as with HIV there appears to be a scientific consensus that (new) malaria vaccine design(s) is the critical stage upon which further improvements in vaccine prospects rests.¹⁵

Animal models for some forms of malaria exist but are generally not considered predictive of human immune responses and hence not particularly useful for guiding human vaccine design. Again, improvement in design will probably rest on relatively expensive human studies with a variety of candidate products.

For both HIV and malaria vaccine development Phase 2b studies in high risk populations may be a less expensive way of gathering information than large Phase 3 efficacy trials but these are still time consuming and relatively expensive.

Thus for both HIV and malaria vaccines, the state of scientific knowledge and the nature of the disease dictate the long-term vaccine development strategies and these require relatively risky and large expenditures. In the past commercial companies have relied substantially on public investments to provide the information for vaccine design.

Introduction issues

As described above, achieving the desired (higher) levels efficacy for HIV and malaria vaccines to be acceptable for routine use, will probably require successive improving ‘generations’ of vaccines. This is itself likely to complicate decisions on manufacturing capacity, and hence the introduction and uptake of these vaccines.

Even if their vaccine candidate has been shown to be effective, manufacturers will be hesitant to invest in high manufacturing capacity if they feel that the product will be replaced rapidly by others, as is highly likely for the early versions of both HIV and malaria vaccines.

¹⁵ <http://www.malariavaccineroadmap.net/roadmap.html>

Manufacturers are used to managing such risks in a 'normal' vaccine market where most of the information for 'design' is generally well known to all. For HIV and malaria the decisions will be made more complicated since there is a paradoxical 'penalty' on being first (or early) to license – the products that demonstrate early how to protect will be the products that teach others how to do better. This situation might engender a 'wait-and-see-what-works-and-then-push-aggressively' attitude on the part of companies that can muster large resources. Countering this tendency will be the prospect that the high price guarantee component of some of the proposed advanced purchase commitments may be used up by early products if companies delay too long. These tendencies may be argued to counterbalance each other, but in fact they complicate decisions with extra layers of uncertainty, to which most companies are averse.

When, and where, to implement partially effective vaccines poses significant policy and strategy questions. These create uncertainty for early demand estimation, supply and procurement decisions. Some of these difficulties were identified in the WHO/UNAIDS/IAVI exercise that encouraged policy makers to anticipate introduction of hypothetical HIV/AIDS vaccines.¹⁶

In the case of malaria, experienced immunization practitioners -- accustomed to vaccine efficacy levels of over 80% -- reacted skeptically to the suggestion in a mid-1990s analysis that a hypothetical malaria vaccine (having low efficacy (<50%) and limited duration) was worth putting into wide use because it would be "cost-effective". Among their concerns was the impact on the credibility of the overall immunization effort.

These cautions are not meant to deter optimism, but rather to illustrate the fact that it is advisable to address introduction issues early. This is particularly true where there are difficult to resolve safety questions regarding vaccine or vaccination strategy. These include for HIV the possibility of vaccines abandoning risk-reducing behaviors, or for malaria vaccines simply shifting the age of disease vulnerability.

Projections of HIV and malaria vaccine development

Various attempts have been made to predict the timelines for HIV and malaria vaccine development. The short discussion below concentrates on predictions by scientists rather than pledges by politicians to attempt to accelerate this process as particularly have occurred for HIV vaccines.

In 1987 a joint committee of the US National Academy of Sciences and its Institute of Medicine predicted that development of a preventive HIV vaccine would take (at least) 5 to 10 years from that date.¹⁷ Over the following years most subsequent predictions – including those now being made – have reiterated the minimum estimate of a decade hence. One year earlier, another committee of the Institute of Medicine (IOM) predicted (on the basis of wide polling of experts) that there was a 50% probability of a malaria vaccine being developed within 10 years.¹⁸ That committee also predicted the development probabilities and times to licensure for about 20 vaccines that were candidates for accelerated development by the US National Institutes of Health. As time has proven, the predictions were reasonably accurate for vaccines that were at that time in late stage development by major vaccine companies, but its estimates for vaccines that were then in the design/early development stages were significantly over optimistic.

Extensive scientific research funding in the years since HIV was discovered make it possible to regard it as the virus about which more is known than any other, in terms of genome, structure,

¹⁶ Esparza, J., Chang, M-L., Widdus, R., et al. 2003 Estimating of "needs" and "probable uptake" for HIV/AIDS preventive vaccines based on possible policies and likely acceptance (a WHO/UNAIDS/IAVI study) *Vaccine* 21: 2032-2041

¹⁷ Institute of Medicine/National Academy of Sciences, 1987. *Confronting AIDS: Directions for Research, Health Care and Public Health*, National Academy Press, Washington, DC.

¹⁸ Institute of Medicine, 1986. *New Vaccine Development: Establishing Priorities Volume 2. Diseases of importance in Developing Countries*. National Academy Press. 432pp.

mode of replication and pathogenesis. However, such knowledge, and that from animal models for human HIV infection, provides incomplete and imperfect guidance when it comes to identifying what the components of an effective protective HIV vaccine will need to be. Comparison of the state of knowledge for design of malaria vaccine candidates included in the above mentioned IOM predictions of vaccine development probabilities and recent reviews, about 20 years later, shows that the advance of knowledge in this field is relatively slow. Optimism from recent Phase IIb trials in Mozambique confirming in children the promise of one candidate vaccine need to be assessed in the context of the overall challenges in arriving at a vaccine which has greater efficacy as have been well laid out by Richie and Saul (2002).¹⁹

Experience thus suggests that predictions of the timeframe required for successful vaccine development are not likely to be accurate where scientific or innovation breakthroughs are required.

¹⁹ Richie, T.L. and Saul, A. 2002 Progress and challenges for malaria vaccines. *Nature* 415: 694-701.

D. Issues reflected in Terms of Reference

D.1. Key research, development, and manufacturing stakeholders in HIV and malaria vaccine development

To focus on the main elements in the terms of reference (namely product development rather than basic research) and to avoid time-intensive judgements about classifying different types of research, this section adopts as a dividing line between 'research' and 'product development' the point at which candidate products enter into clinical trials.

It draws upon a number of intermediate sources to identify the designers or manufacturers of products in clinical testing as HIV or malaria candidate vaccines. These are listed in Annexes 2 and 3 respectively.

Noteworthy among current players are:

- Research institutes involved in translating concepts for vaccines into candidate products i.e., vaccine prototype design;
- Small biotechs, mostly but not only in industrialized countries, often working with PDPs;
- Larger commercial R&D based vaccine companies, working sometimes on their own but also often with research institutes or small biotechs and with PDPs.

Other players are key but are less targeted by advanced purchase commitments

They include:

- Research institutes conducting basic and applied research for product concepts, mostly but not only in industrialized countries;
- International organizations;
- Pilot lot producers, where non-commercial;
- Institutes collaborating in clinical testing of candidate products in both industrialized and developing countries.

Although candidate products will be tested in disease endemic countries (DECs) with high incidence and will need to be passed by their regulatory agencies, officials from these DEC regulatory agencies have not been major actors in development efforts to date. This is attributable in large part to the limited capacities in DECs for overseeing new product trials, and evaluating new product manufacturing technologies. Such engagement as has occurred has most often been via participation in WHO meetings.

In light of the perceived shortages in translational research/production process development expertise, and clinical trials capacity in disease endemic countries, a preliminary listing of such capacities has been started in Annexes 4 and 5.

D.2. Current levels of public and private funding and expenditure on vaccine R&D

This section focuses on the ultimate source of funding for HIV and malaria vaccines R&D. It should however be recognized that organizations like the product development partnerships referred to above 'add-value' in ensuring that the resources provided through them are used effectively.²⁰

Readers are cautioned that the figures quoted below derive from different data gathering exercises for HIV/AIDS and malaria, hence they results are not be precisely comparable as the respective definitions and inclusion criteria undoubtedly differed. The differences however are probably small enough for general conclusions to be drawn.

As two extensive exercises are underway to document resource flows for HIV and malaria vaccine R&D respectively, the data reported here should be updated when full results from those efforts^{21, 22} are available.

Funding sources for HIV and malaria vaccine research and development

Information on original sources of funds for HIV and malaria vaccine R&D is shown in Tables 3 and 4, respectively. The names of funders are included in the respective tables if they have been identified as providing some resources (e.g., to EMVI, IAVI or specific projects) even where complete information on their funding levels was not available.

Of overall funding for HIV vaccine R&D in 2004 from public sources (approximately US\$ 608 million), the USA provided 86.5% versus 8.3% from Europe. Generally, US funding is overwhelmingly via the US-NIH (particularly the NIAID which provides a broad array of mechanisms²³) and US-DOD.

Among developing countries India and the Republic of South Africa (through the South African AIDS Vaccine Initiative, SAAVI) are providing significant support for HIV vaccine development. Brazil, Thailand, and China are also known to be supporting national activities in HIV vaccines development.

The recent consultation group for the Global HIV Vaccine Enterprise has recommended that support for HIV vaccine R&D be roughly doubled to US\$ 1.2 billion annually.

Of estimated funding for malaria vaccine R&D in 2003 from public and philanthropic sources, the USA provided roughly 88% versus around 12% from Europe. One estimate places the total expenditures on malaria vaccines for 2004 at US\$ 84 million.²⁴

Funding for malaria vaccine R&D in 2004 would thus appear to be around 15% of that for HIV vaccine R&D.

Even though information on funding sources gathered in this brief study is incomplete, missing data is unlikely to shift the picture significantly, as all major sources are probably captured.

Given the relative size of their aggregate economies, overall funding of HIV and malaria vaccine R&D by European and other industrialized countries appears to be at disproportionately low

²⁰ Pfitzer, M. 2004. Demonstrating value: Performance metrics for health product development public-private partnerships, pp159-163 in Widdus, R. and White, K. Combating diseases associated with poverty: Financing strategies for product development and the potential role of public-private partnerships. Initiative on Public-Private partnerships for Health, Global Forum for Health Research, Geneva. 214pp.

²¹ Public and philanthropic investments in preventive HIV vaccine and microbicides: 2000 to 2004, AVAC/AMD/IAVI/UN AIDS Study. A full report and private/industry funding should be available in May 2005.

²² Global Funding for Malaria Research and Development Study; commissioned in early 2005 by the Malaria Vaccine Initiative at PATH, due for completion in July 2005.

⁹ <http://www.niaid.nih.gov/daids/vaccine/funding.htm>

²⁴ Hoffman, S. 2004. Save the children: Creating a malaria vaccine will be tough. Nature 430: 940-941

levels compared to that from the USA. This issue should be examined in more detail when country specific figures are available.

Table 3: Public sector funding sources for HIV vaccines research and development

	Estimated US\$ (000s)			
	2000		2004	
		%		%
Europe European Commission Denmark France Germany Ireland Netherlands Norway Sweden United Kingdom: - MRC - DFID	24,000		50,000	
USA US – NIH US – DOD	271,000		526,000	
Other public sector (not USA or Europe) Australia Brazil Canada China India Japan Republic of South Africa Thailand	12,000		29,000	
International organizations: WHO/UNAIDS	1,800		1,800	
PROVISIONAL TOTALS (Public sector)	308,000		608,000	

Source: Preliminary information from: Public, Philanthropic and Private Sector Investments in Preventive HIV Vaccines and Microbicides: 2000-2004, by the HIV Vaccines and Microbicides Resources Tracking Group (AVAC/AMD/IAVI/UNAIDS), anticipated completion in May 2005.

Table 4: Funding sources for malaria vaccine research and development

	US dollars (000s)					
	1999	2000	2001	2002	2003	2004*
Europe						
European Commission	4,250	4,250	4,250	4,250	4,250	
Denmark						
Germany						
Ireland						
Netherlands						
Norway						
Sweden						
United Kingdom						
- MRC						
- DFID						
- Wellcome Trust						
USA						
US NIH/NIAID	28,000	31,700	28,700	29,600	33,000	
US – DOD (NMRC & WRAIR)	4,856	5,774	8,496	7,510	5,889	
USAID	3,000	2,980	4,250	4,700	4,700	
Bill & Melinda Gates Foundation/MVI	334	2,497	13,140	12,799	14,046	
Other malaria vaccine						
Rockefeller Foundation						
Australia						
Canada						
Japan						
Ministry of Science and Technology						
Ministry of Health and Welfare						
International organizations (TDR/WHO)	1,210	969	860	400	350	
Provisional totals	42,304	49,168	60,844	62,659	65,735	84,000²⁵

Source: The State of Malaria Vaccine Development at the website of the Malaria Vaccine Technology Roadmap, ²⁶ and Hoffman, S. 2004 (see reference below).

²⁵ Hoffman, S. 2004. Save the children: Creating a malaria vaccine will be tough. Nature 430: 940-941

²⁶ (<http://www.malariavaccineroadmap.net/roadmap.html>)

Private sector funding sources for HIV and malaria vaccine R&D

Commercial funding

Commercial funding sources for vaccine R&D comprise funds allocated from pharmaceutical company revenues and those made available by venture capital investors. In general, the latter are considered as somewhat more speculative and hence likely to be more common at earlier stages of product development. However, both ultimately chose areas likely to yield return on investment.

Precise levels of R&D activity and expenditure within pharmaceutical companies can only be estimated from in-depth investigations not possible given the short duration of this project. However, the HIV Vaccines and Microbicides Resource Tracking Working Group,²⁷ anticipates producing some estimates in early May. (See Section B).

Of major pharmaceutical companies producing vaccines it is believed that most have some level of programmes in HIV. For malaria the engagement of major vaccine companies appears to be limited to GlaxoSmithKline Biologicals collaboration over nearly 20 years with the US Army WRAIR and recently with Malaria Vaccine Initiative at PATH for use in infants and children.

In development of both HIV and malaria vaccines, a number of small 'biotech' companies have various concepts and candidate products in applied research, translational research, preclinical research and Phases I and II clinical testing. The VaxGen company carried a early HIV vaccine candidate, AIDSVAX, through a phase III trial principally in the USA and Thailand, at considerable cost.²⁸ These 'biotech' companies may have funding from government and philanthropic grants (sometimes via PD PPP channels), private capital, venture capital and financing arrangements with larger pharmaceutical companies on specific products/projects.

It is interesting to note that certain private businesses in countries heavily affected by HIV/AIDS like South Africa have contributed to funding HIV vaccine development, e.g., the RSA power company, Eskom, contributes to the funding of the SAAVI. Relative to public sector funding this support, while welcome, is very rare and modest in level.

Philanthropic funding

In 2002, the Bill & Melinda Gates Foundation allocated US\$ 100 million to IAVI, which was all disbursed by the foundation in that year. A number of other private philanthropic and commercial organizations provide support, generally on a relatively small scale, to IAVI.

²⁷ AVAC/AMD/IAVI/UNAIDS

²⁸ Francis, D. P. 2004. The costs of developing vaccines: Case study of VaxGen's HIV candidate vaccine. Pp 188-191 in Widdus, R. and White, K. Combating diseases associated with poverty: Financing strategies for product development and the potential role of public-private partnerships. Initiative on Public-Private Partnerships for Health, Geneva. 214pp.

D.3. Current strengths and weaknesses in the vaccine development and introduction pathway for developing countries

Table 5: Strengths and weaknesses of the current 'system' for vaccine development and introduction into developing countries

Step	Strengths	Weaknesses
Basic research	New science has expanded knowledge, 'tools', and possible approaches	Low funding for national disease burden studies in poorer countries hinders policy making
Applied research	New science has expanded knowledge, 'tools', and possible approaches	
Translational research	More 'tools' available	Shortage of expertise and low funding for process development/pilot lot production
Preclinical research		Predictive animal models not available for many human vaccines, inc. HIV, malaria, and TB
Production process development	Increasing capacities in contract bio-pharmaceuticals manufacturing	Shortage of expertise.
Clinical research: Phase I		Shortage of capacity in poorest disease endemic countries (DECs)
Clinical research: Phase II		Shortage of capacity in poorest disease endemic countries, especially for Phase 2b
Clinical research: Phase III		Shortage of capacity in poorest disease endemic countries, especially for Phase 3
Regulatory assessment	Some new pathways emerging e.g., via EMEA	Low capacity in poorer DECs in trials oversight and assessment of new products not used in rich countries
Manufacturing	Bio-pharmaceuticals manufacturing capacity increasing, including developing countries	Lower interest in preventive vs. therapeutic products. Shortage of expertise
'Utility' studies	Increasing capacities, e.g., International Vaccine Institute, Seoul, S. Korea	Limited capacities in poorer DECs. Needs for policy not anticipated, hence delays
International policy guidelines	Responsibility lies clearly with one agency -- WHO	General process of policy formulation not defined, but rather reactive, and <i>ad hoc</i> . Required studies not defined in advance for product sponsors
National policy formulation		In poorer DECs often delayed awaiting Int. guidelines and usually donor resource dependent. Delays due to lack of disease burden information
Resource mobilization	Funds increasing (GAVI/IF) Potential International Finance Facility for Immunization	Available funds for existing products and particularly 'infrastructure' still inadequate

(Continued)

Table 5: Strengths and weaknesses of the current 'system' for vaccine development and introduction into developing countries

Step	Strengths	Weaknesses
'Procurement'	New funds could allow multi-year contracts	For poorest countries: historically inaccurate demand projections; unpredictable actual purchases; short-term/annual perspective and contracts; no performance comparisons possible. Unlinked to new vaccine availability. Lack of expertise in complex/multi year procurement processes.
Implementation	Funds increasing somewhat	Weak infrastructure for reaching rural/poor within poorer DEC's
Pharmaco-vigilance	Safety issues usually well studied in industrialized countries	Weak in majority of poorer countries, hence logistical and ethical challenges for rapid new product introduction.

D.4. Existing incentives and other instruments supporting vaccine R&D and which could support future introduction

The most useful mechanisms for accelerating development and introduction of new vaccines to poorer countries have been increasingly debated in recent years. Experience with the mechanisms used to encourage development and supply of products to combat rare or 'orphan' diseases in affluent countries has been well reviewed (see Milne, Kaiten, and Ronchi, 2002²⁹), but is not exactly analogous. In the case of 'orphan' products for affluent countries some real potential for revenue existed (although smaller than that with products for common health problems). National governments in industrialized countries have a direct obligation to their citizens for taking action in this situation, and they also have jurisdiction over incentives like clinical trials protocol assistance, and (domestic) market exclusivity. The situation becomes more complex when incentives and rewards need to operate across national boundaries and the potential for revenues is more questionable.

Before identifying the various 'instruments' that have been proposed to accelerate vaccine introduction into poorer countries or speed the development of vaccines needed specifically to combat the diseases predominantly associated with poverty, it is advisable to examine why such remedies are necessary.

The low level of commercial vaccine development for diseases associated poverty and the relatively low interest in many vaccine companies in supply for the poorer countries are frequently said to be the result of "market failure". However, commercial vaccine developers/producers are acting in a rational way – pursuing reasonable revenues and profit, which are essential for their continued operations. The situation could equally be described as public policy failure. Failure to recognise the public health – and monetary – value of vaccines resulting in excessive price sensitivity and low allocations of bilateral aid have deterred most interest in vaccine markets for developing countries, especially the poorer ones.³⁰ These failures are compounded by insufficient investment in (or aid for) disease surveillance systems so slow policy formulation further delays introduction into poorer countries and growth of revenues.

Thus greater willingness to pay for the various facets of disease control in poorer countries – not only product procurement but also delivery -- is the simplest long term remedy to low commercial engagement. With a reasonable level of attractive market established, some commercial innovators would seek out an attractive 'niche', even if it were not a 'blockbuster'.

Where acceleration of introduction of 'new' vaccines into poorer countries has been addressed (by for example GAVI/Vaccine Fund) it has mostly focused on the backlog of already licensed products such as Hepatitis B, Hib, and combinations, and increasingly system strengthening. Continuing pledges for these mechanisms by the Gates Foundation, Canada, Norway and the UK will help these activities close the 'rich/poor gap' on these more established products.

In the last few years the Gates Foundation has also sponsored accelerated development and introduction planning for vaccines for against rotavirus diarrhoea, pneumococcal pneumonia, and meningitis A. For the first two, recently licensed vaccines and likely new competitors offer over the next few years clear opportunities to work towards faster introduction to poorer countries. These are discussed in the following section (D.5.). The Foundation has also provided support for development of vaccines at various earlier stages of development against different diseases: HIV/AIDS, Malaria, Dengue, Japanese Encephalitis and Human Hookworm.

²⁹ Milne, C., Kaiten, K., and Ronchi, E. 2002. Orphan drug laws in Europe and the USA: Incentives for research and development of medicines for diseases of poverty. Prepared for Working Group 2 (International Public Goods for Health) of the WHO Commission on Macro-economics and Health.

³⁰ The decision by GlaxoSmithKline to license its new rotavirus vaccine first in Mexico, a 'developing country' (albeit a relatively affluent one) reflects innovative thinking on how 'markets' and global public health needs can be addressed, However, this product will have a market in industrialized countries.

For both established and more recent vaccines the funding that could be made available through the proposed International Financing Facility for Immunization (IFFI) would be invaluable if this mechanism is approved.

Moral pressure to do more to help developing countries achieve the Millennium Development Goals by 2015 appears to be increasing promises of bilateral aid. However, other remedies are worth examining.

The range of existing or proposed interventions to accelerate the 'availability' (development) or 'accessibility' (actual delivery) of drugs and vaccines can be grouped in various ways such as that presented in Table 6, Parts A and B.³¹ Most of the approaches listed are directly applicable to vaccines or have vaccine-related counterparts.

It is important to recognise that many of the interventions that are listed in Table 6 only address one aspect of the overall chain of vaccine development and introduction outlined earlier and presented in Figure 1. They may be potentially beneficial on that aspect but will not necessarily be a 'magic bullet' to fix all problems.

When considering approaches to accelerate the progression of a particular product down the development and introduction pathway it is also important to consider the point at which it is currently located and the particular barriers which immediately block its progress. Those interventions that address these barriers directly are the most certain to have an impact.

The author believes that most serious analysts of vaccine development and introduction -- and the broader question of access to medicines -- for poorer populations believe a comprehensive approach is necessary. Such a comprehensive approach would include:

- 'Push' interventions, to accelerate candidate product design/development;
- 'Pull' interventions, that variously provide economic reward and assure product use, both directly through purchase and indirectly by establishing the delivery systems that mean products can reach maximum number of recipients;
- Product development partnerships, i.e., 'brokers' anticipating needs, engaging necessary players and filling gaps, as needed, to expedite the passage of candidate products down the development and introduction pathway; and
- Support for system strengthening as a whole (as described in the Background section, C.1.).

Vaccine development partnerships, particularly those using a portfolio approach, are judged a promising method for accelerating 'neglected' product development (Widdus and White, 2004).

³¹ From Widdus, R. 2004. How public-private partnerships manage intellectual property and how this might improve access to medicines, Prepared for a Bellagio Dialogue on Access to Medicines convened by the International Center for Trade and Sustainable Development and UNCTAD, 12-16 October 2004. Available at [www. http://www.iprsonline.org/unctadictsd/bellagio/docs/Widdus_Bellagio3_revised.pdf](http://www.iprsonline.org/unctadictsd/bellagio/docs/Widdus_Bellagio3_revised.pdf)

Table 6: Proposed Interventions to Promote Access to Drugs and Vaccines - Part A: Availability

‘Push’ Interventions		‘Pull’ interventions
To lower costs and risks of research and development	To remove barriers in the development ‘pipeline’	To provide incentives for development and manufacture, by creating a market, providing other economic rewards or removing economic deterrents
<p>Basic research funding (from government or philanthropy)</p> <p>Grants for product development</p> <p>R & D tax credits to companies</p> <p>R & D expense ‘write-offs’</p> <p>Tax credits to investors</p> <p>Establishment of R & D capacities in endemic situations, e.g., Phase III trial sites</p> <p>Protocol assistance, as per U.S. Orphan Drug Act</p> <p>Support for R & D to identify new indications for existing entities:</p> <ul style="list-style-type: none"> - Financial - Through mass screening facilities <p>Consortia (Public; private; or public/private)</p> <p>‘horizontal’ – discovery</p> <p>‘vertical’ – development/manufacturing</p>	<p>Regulatory harmonization (scientific and procedural)</p> <p>Expediting regulatory/licensing processes</p> <p>Lowering regulatory fees for specified product categories</p> <p>Simplification (not lowering) of standards</p> <p>Protocol assistance</p> <p>Setting ethical guidelines for conduct of research involving human subjects, and or international collaboration</p> <p>Strengthening regulatory capacity in poorer disease endemic countries</p> <p>Possibility of regional regulatory collaborations</p>	<p>Improved delivery of existing drugs and vaccines</p> <p>Identification of public health priorities for new projects</p> <p>Product specifications/contingent recommendations for use</p> <p>Recommendations for use (earlier)</p> <p>Market assessments</p> <p>Patent extension</p> <p>Patent ‘exchange’ (extension on another product)</p> <p>Market exclusivity</p> <p>Prizes (for first to meet specified product characteristics)</p> <p>Market ‘assurances’</p> <ul style="list-style-type: none"> - Purchase funds (for existing and/or future products) - Contingent loans and credits - Minimum price guarantee ‘cost-plus’ formulas - Requisition to buy <p>Legislation on product liability litigation</p>
<p>Proposals to manage ‘orphan’ and ‘neglected product R & D:</p> <ul style="list-style-type: none"> ▪ US HHS Secretary’s Vaccines Work Group, 1978: National Vaccine Commission ▪ US Institute of Medicine: 1986, National Vaccine Commission; 1993, National Vaccine Authority ▪ Ad Hoc Committee on Health Research and Development, 1996: Health Product Development Facility or Alliance (p.xxxvii) ▪ At GAVI R & D discussion, 1999: Public-private vaccine partnership ‘umbrella’ for development and/or manufacture ▪ Creation in late 1990s to early 2000 of numerous not-for-profit entities to foster public-private partnerships in product development 		

Table 6: Proposed Interventions to Promote Access to Drugs and Vaccines - Part B: Accessibility

Interventions addressing product quality, rational selection and appropriate prescription and use	Interventions addressing supply/logistics	Interventions addressing economic factors
<p><u>Assurance of quality</u> Strengthening national regulatory agencies and their enforcement capacities</p> <p>Implementation of measures against counterfeit and ineffective medicines</p> <p><u>Rational selection</u> Designation of national 'essential' drugs lists</p> <p>Identification of optimal formulations/packaging</p> <p>Ethical criteria for drug promotion</p> <p>Consumer education</p> <p><u>Use</u> Training in appropriate use - prescribers - dispensers, drug sellers - patients and community</p> <p>Consumer education - compliance/adherence</p> <p>Regulation of drug and vaccine provision through private providers and monitoring of compliance (NB: Private sector distribution in many countries at 50-90% of markets)</p> <p>Monitoring consequences of misuse, e.g., antibiotic resistance, and educating on its dangers</p> <p><u>Consumer knowledge and health behaviour</u> Consumer education (for appropriate use)</p>	<p><u>Reliable sources of supply</u> Preparation of demand/uptake estimates for global needs, to predict and coordinate necessary production capacity requirements</p> <p>Training in preparation of demand estimates at national level</p> <p>Multi-year predictions/contracts</p> <p>Training in procurement procedures (to secure fair prices)</p> <p>Brokering by international organizations between potential suppliers and 'consumers' to ensure reliable supply</p> <p>'Local' manufacturing</p> <p><u>Availability at point of use</u> Market consolidation (bulk procurement) to facilitate supply to previously unserved populations (e.g., UNICEF, PAHO procurements)</p> <p>Training in design/management of distribution systems</p> <p>Expand pharmacy services in rural areas</p> <p>Contracting for private sector delivery systems</p> <p>Consumer education (to increase demand)</p>	<p><u>Resources</u> Allocation of adequate government financial resources</p> <p>Market segmentation (for procurement for poorest countries) and price tiering by suppliers</p> <p>Targeting of public financing to neediest</p> <p>Cost-recovery schemes</p> <p>Cost-sharing schemes/insurance</p> <p>Advocacy to policymakers particularly on 'value' of prevention</p> <p>Social marketing to 'consumers'</p> <p>Debt relief, loan contingencies</p> <p><u>Cost</u> Tax credits to encourage donations by industry</p> <p>Support for new methods to lower production costs</p> <p><u>Pricing policies and controls</u> Encourage generic drug use/competition</p> <p>'Compulsory' licensing (Innovation may be inhibited)</p> <p>Parallel importation (Innovation may be inhibited)</p> <p>Government price controls (Innovation may be inhibited) - cost-plus - reference pricing - profit/return on capital</p> <p>Tiered/concessionary pricing based on market segmentation</p> <p><u>Price at point of use</u> Elimination of import taxes</p> <p>Reduce distribution margins that increase consumer prices (by up to 80% in some cases)</p>

D.5. Implications for the design of advance purchase commitments and other instruments and support to accelerate vaccine development and introduction to poorer countries

Advance purchase commitments can take many forms. The recent discussions of mechanisms to reassure potential product commercial developers of a potential 'market' for products in early development (such as HIV or malaria vaccines) have unfortunately been made slightly confusing by a lack of uniformly used terminology covering the range of situations around vaccine procurement that need to be considered.

'Inferred' advance purchase commitments

An 'advance purchase commitment' can be inferred from a pattern of purchasing vaccines which establishes a reasonable expectation that future purchases are predictable.

This is the case for the purchases of recommended childhood vaccines in industrialized countries, beyond the current negotiation which is usually an annual cycle. Manufacturers rely on such predictable purchasing behaviour patterns, even though there is no long term written contract or tender. They commit to anticipatory investment in manufacturing and even to investment in new/updated production capacity for future years, without formal agreements, despite uncertainties on awarding the ultimate supply contracts.

For many decades the developers of vaccines in affluent countries have also operated upon the unwritten understanding that a new safe, efficacious product for a significant disease would be used by public health authorities, and this would result in revenues from government or other purchase – even though there was uncertainty what the specific recommendations for use and volumes purchased would be. Since recommendations for vaccine use and vaccine procurement in many countries are handled by governments, the nature of this informal, advance purchase commitment is much more a relationship between developer and government than for sales of other health products where the consumer or physician is more involved in the decision to use. It rests largely on the developer observing a consistent pattern of government purchasing behaviour signalling reliability and commitment to vaccines as a part of public health.

In the USA, the Vaccine for Children Act, in the early 1990s, established not only existing but also new vaccines, if recommended by the Advisory Committee on Immunization Practices, as a Medicaid 'entitlement' for around 60% of US children. The legislation was not initially favoured by some vaccine developers/manufacturers (mostly because it capped prices of existing vaccines). However, it is now regarded more favourably because of its provisions of guaranteed purchase and hence more rapid uptake for new vaccines, despite the fact that there is no specification for new product characteristics, volumes to be purchased or price.

In the UK, a non-contractual 'promise to purchase' accelerated commercial development of a conjugate vaccine for type C meningitis (*Neisseria meningitidis* type C) (ref D. Salisbury, UK Department of Health, personal communication, reference being sought). In this situation, the arrangement was not subject to a formal offer or contract specifying product details. Various companies pursued their own approaches, each slightly different, with most meeting licensing and supply deadlines. This inferred advance purchase commitment to encourage vaccine development (rather than for an existing vaccine), operated well for a candidate product for which the effective design was already scientifically established and the production technology well known.

The companies that have introduced new vaccines in industrialized countries over the last few decades have initially installed production capacity conservatively. They have built plant for the market which was predictable – in many instances usually for volumes for only for their domestic or at best industrialized country markets.

Procurement of vaccines for poorer countries – historically an unattractive market

An argument made recently for 'advance purchase commitments' for early-stage vaccines for diseases of developing countries is that the market was "unpredictable". This claim in fact has two facets. The capacity of international public sector agencies to predict reliably the annual demand for traditional vaccines for developing countries has been poor. Even worse has been the capacity to predict the year-by-year uptake of new vaccines (such as Hb-combinations or Hib). Ironically, the 'market' (revenues) from vaccines for developing countries has been all-too-predictably low and commercially unattractive to many suppliers.

Because of these and other weaknesses in the 'procurement'/uptake planning system for vaccines for developing country, vaccine producers (including those that are also new product developers) generally see remedy of these shortcomings – generally expressed as the low 'value' placed on vaccines by the public sector -- as the highest priority in advance purchase commitments, when the term is used generally. Multi-year contracts for supply of underused and older 'recent' vaccines (e.g., Hepatitis B) at reasonable prices along with serious joint planning for the rapid introduction of 'recent' vaccines would go a long way to making the business of vaccine supply to low income countries more commercially attractive.

Regarding the supply and development of new vaccines needed in developing countries, we need to distinguish two categories. For some, e.g., rotavirus and pneumococcal vaccines) there will be a profitable market in industrialized countries, and the main issue is ensuring manufacturing capacity of sufficient scale to supply the larger needs. Initial scaling of capacity has historically tended to be conservative (for the much smaller industrialized country market) for two reasons: "Uncertainty" of reasonable returns from poorer markets and historically long and unpredictable processes for uptake for such supply. Investment in production capacity that turns out to be unused ('excess') is financially wasteful and therefore avoided. Increases in production efficiency (higher yield, lower unit costs of production) has historically easily kept pace with the slowly rising, highly price-sensitive market, albeit not public health need.

In terms of product volume, vaccines for HIV/AIDS will mostly be needed in developing countries. However they probably rest – uncertainly – somewhere between the prospects for a reasonably profitable industrialized country market (if a 'global' vaccine emerges with high efficacy and recommendations for wide use) and prospects of very limited industrialized country revenues (if they have low efficacy and recommendations for use target limited high-risk group). Unknowns include scientific issues (if different 'clade' versions will be needed) and uncertain policies that will depend on vaccine efficacy. Consequently most major vaccine companies have some level of activity in HIV/AIDS vaccines but this is usually low for a range of reasons, particularly the state of scientific knowledge to guide design.

GlaxoSmithKline-Biologicals has kept some presence in the malaria vaccine development field through a long-standing collaboration with the US Department of Defence Walter Reed Army Institute of Research, probably with an eye to a military or travellers market. However, this has not been a major investment compared to other company projects.

Development of vaccines (such as those for leishmaniasis and schistosomiasis) which have no or extremely limited prospects of a profitable market in affluent countries are even more unattractive to potential developers/producers as – from experiences described above – they expect slow formulation of international guidelines, delayed uptake and low prices. For many of these types of vaccine the scientific knowledge is the main challenge but they are unlikely ever to elicit much commercial interest, except possibly in large developing countries where these diseases are endemic.

Given that there does exist a low activity in development of vaccines for HIV and malaria it could be argued that there is some level of inferred purchase commitment for these products but for obvious reasons this seems to derive mostly from the (better) prospects for purchase in affluent markets than where the public health need is greatest.

Long term supply contracts for existing (or new) products

Because of the long lead times in vaccine production and amortizing investment in manufacturing plant producers prefer multi-year supply contracts.

These types of long-term supply contracts can be thought of as one type of 'advance purchase commitments'. Contract manufacturing of biologicals is becoming more common (see back issues of Genetic Engineering News), but probably the US Department of Defence has the longest history of such arrangements. A variety of contractual mechanisms can be used for manufacturing of proven products, including 'fixed-price', 'cost-plus', and other approaches.

More rarely contracts have been considered for product development. These are known mostly for military equipment development and are often 'cost-plus' arrangements with close financial auditing. Few instances of contracting for health product development are known probably because of the unpredictability of scientific breakthroughs. Two sources of information that could be pursued further are the historical US Department of Defence contracting for vaccine procurement and the recent experience arising from the legislation in the USA on BioShield. However, this was not possible in the scope of this project.

Procurement practices that split supply contracts can be useful in helping maintain an optimal number of suppliers competing on price. Winner-take-all strategies in procurement are not only typically disliked by most suppliers but also risky for purchasers, as they can result in producers leaving the (vaccine) business.

In 2004 UNICEF instituted 3 year contracts for its vaccine procurement.

APCs as a component of public-private planning for introduction of recent (and possibly late development-stage) products

Another type of advanced purchase commitment has been discussed which could accelerate the introduction of recently licensed vaccines into developing countries and in the short-term possibly accelerate the late stage development of competitor/alternative products. This would apply to products licensed relatively recently usually in industrialized countries but which are also needed in developing countries.

As noted above the use of these 'global' products in developing countries is typically delayed by the conservative decisions of manufacturers on the size of production plant. Plants designed with capacity to meet only demand from industrialized countries limit supply and forego any economies of scale that can reduce cost-per-dose. Hence possible prices remain high, further delaying introduction. APCs for 'recent products' could build confidence of vaccine developers/manufacturers of a future market for vaccines in development. They could also yield other benefits, such as more predictable uptake/demand scenarios, assured supply capacity and better prices.

Some steps towards collaboration with industry on accelerated development and introduction plans (ADIPS) have been taken with rotavirus and pneumococcal vaccines, and are planned for Hib. While the processes of different sectors learning how to collaborate efficiently, estimate demand and uptake, and establish optimal procedures, e.g., on sole-suppliers while fostering future competition, are still in their early stages there are some clear practical opportunities to learn how advanced purchase commitments might be

formulated for mutual benefit. These are described under Section E: Conclusions and recommendations.

Another approach to planning the introduction of late stage products has been adopted by the Meningitis Vaccine Project of PATH which is targeting a conjugated polysaccharide vaccine against *N. meningitidis* type A, mainly for the meningitis belt in Africa.³² Under this approach there have been negotiations with a developing country manufacturer (Serum Institute of India Ltd.) to be the 'recipient' of a new conjugation technology in return for an understanding on the future price of the product being low enough for the target countries to sustain. Work under the project includes disease surveillance and frequent communication with prospective end-users. The approach was initiated in 2000 and, while it is dependent on a heretofore untested pathway to making new/late development-stage vaccines available to developing countries, it appears to be progressing well.

'Advanced Markets', a proposed advance purchase commitment, or 'offer' for early development stage vaccines, such as malaria or HIV/AIDS

An 'Advanced Market'-type mechanisms, as proposed by the authors at the Center for Global Development, Washington, DC, USA, under which an 'offer' is made by potential purchasers (sponsors) to pay a set price per course of vaccination for a product (or improving products) if it/they meets certain specifications, up to a specified monetary limit. Sponsors would retain the right to switch to improved generations of vaccines so no individual developer/manufacturer is assured of any particular level of revenue even if first to market. The promotion of the proposal has been overwhelmingly based on its suggested effects for vaccines for HIV, malaria and tuberculosis and it has received some general support as sending a desirable signal on these products.

Recent discussions of the 'Advanced Markets'-type of advance purchase commitment in fact started around the Sabin Vaccine Institute colloquium held at Cold Spring Harbor, New York, 5 – 7 December 1997. That meeting identified many of the issues and reservations³³ still being debated as the CGD tried to finalize its Working Group report prior to the upcoming April meeting of Finance Ministers in Washington, D.C.

A range of concerns, as yet unresolved, have been raised on the practicality of the Advanced Markets-type of proposal for early development-stage vaccines such as those for HIV and malaria for which it has been mostly advocated.

Discussion of these concerns can be found in:

- The report of the Sabin Vaccine Institute 1999 colloquium referenced previously.
- Discussion forum on advanced purchase commitments as proposed by the Center for Global Development archived at the website of the WHO Commission on Intellectual Property, Innovation and Health (www.who.int/intellectualproperty/forum/en/Discussion2_text.pdf) (64pp).
- In 'Making Practical Markets' for Vaccines: Questions and Concerns about the CGD Drat, by Donald W. Light, Princeton University, NJ, USA., formerly a CGD Working Group Member.
- In 'The Global HIV Vaccine Enterprise, Malaria Vaccines, and Purchase Commitments: What is the Fit? A Response to (the CGD Proposal) 'Making Markets' and Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases' by Kramer M. and Glennerster, R. Princeton University Press, 2004, 152pp. Submission to WHO Commission on Intellectual Property, Innovation and Health, by Andrew Farlow, Department of Economics, Oxford University, UK. 191 pp.

³² See www.meningvax.org

³³ Muraskin W. 2001. Vaccines for Developing Economies: Who will Pay? Albert B. Sabin Vaccine Institute, New Canaan, CT, USA. 176 pp.

- The Right Tool(s): Designing Cost-Effective Strategies for Neglected Diseases Research, by Stephen Maurer, University of California at Berkley, CA, USA. Submission to WHO Commission on Intellectual Property, Innovation and Health. 125 pp.

While most support for the idea of the Advanced Markets-type of advanced purchase commitment is general, concerns expressed are wide ranging and often argued in specific detail on what has been proposed. In many instances they relate to the way in which an AM-type APC for early stage vaccines would need to be implemented, which only becomes apparent when the proposed legal arrangements or “Term Sheets” are examined in detail.

Concerns fall into the following categories:

- Questions and disagreements on the correct concept/model for early vaccine design/innovation;
- Doubts on its utility in changing commercial decisions on whether to engage, especially heavily in early design experimentation/development stages where uncertainties are greatest, and where traditionally public investment aids design ;
- Feasibility of implementation, particularly because of the different types of uncertainty which surround desired products that are in the design/early development stage. These uncertainties include: setting product specifications e.g., for efficacy when there is not now consensus on appropriate trial end-points or what will be a usefully efficacious design; on what will be the production technology and cost of production; when will the products emerge and how quickly might they be replaced; the likelihood of companies signing onto the requirements that restrict their management of their existing and (particularly) future intellectual property. Other concerns on implementation relate to the proposed management structures, and in particular how they would relate to sponsors and existing organizations with responsibilities for decisions relating to global vaccination policy;
- Economic and modelling assumptions: these concerns revolve around setting the promised price so that companies are adequately motivated but not overly so into wasteful behaviour, and/or not eventually overpaid; the correct assumptions for cost of capital/discounting rates, time to product emerging, and other factors;
- Credibility; particularly in the light of historical and current vaccine purchasing behaviour for the poorer countries (that undervalues vaccines) and that the ‘promise’ if put in place ‘politically’ could also be dismantled, with redress only possible through difficult and costly legal action against governments. For others its credibility is undermined by alleged failure to put it in the context of other needs and opportunities for control of diseases associated with poverty, particularly investing in better delivery systems;
- Analytical rigour of proposal development process; including concerns on the limited expertise of the authoring group in vaccine development and pharmaceutical decision making; and in the handling of dissenting views;
- Potential negative consequences: including specific fears that the combination of a volume-limited high price and a major company with a significant lead over other candidates might actually cause some developers to abandon the field; also more general fears that some formulations of specifications might discourage innovative approaches;
- Appropriateness, given:
 - The potential for distracting attention from other, potentially more useful, (push) interventions addressing the specific challenges and key actors at the early design stage where development of future HIV and malaria vaccines is currently located; and
 - The potential for distracting attention from other urgent vaccination/vaccine development needs that could provide benefits earlier.

In a paper submitted for publication, Towse and Kettler have discussed advanced price or purchase commitment of some of the sorts outlined above.³⁴ They conclude that a range of issues should be carefully considered in deciding whether APCs should be attempted and if so how they are designed. These in many ways mirror the concerns expressed about the potential usefulness of the proposed Advanced Markets-type approach for HIV, malaria and other design/early development stage vaccines.

They see the following as critical factors for utility:

- Credibility;
- Setting the specifications [correctly];
- Getting the price right;
- Provisions for second and third entrants;
- Ensuring use; and
- Achieving a balance between 'push' and 'pull' incentives.

The author admits to some sympathy with certain of the concerns expressed about the Advanced Market-type APCs for early stage products. However, the concerns are listed here not to discourage further consideration of this sort of APC but to direct discussion towards the unresolved questions. As recommended below the 'due diligence' needed in further assessment of APCs should also address the broader question of what sorts of APCs or other interventions are most appropriate for the vaccine categories listed at the outset: existing, but still underused vaccines; recently licensed vaccines; late-development stage candidate vaccines; and design/early-development stage candidate vaccines.

³⁴ Towse, A. and Kettler, H. In press. Advance price or purchase commitments to create markets for treatments for diseases of poverty: lessons from three policies.

E. Conclusions and recommendations

The charge for this study was to survey the development and introduction of vaccines into developing countries, including future vaccines against HIV and malaria, and to highlight the implications of that survey for those considering advanced purchase commitments.

1. Situation overview

The situation can be characterised as follows:

- A wide range of opportunities exist to save lives in developing countries through the use of existing vaccines (many of which are not being fully utilized) or the development of new vaccines, candidates for which are at various stages;
- A wide range of interventions, including different sorts of 'system strengthening', exist that could – with varying degrees of certainty – accelerate the development and introduction/utilization of vaccines in developing countries. These include advanced purchase commitments (APCs);
- One specific type of advanced purchase commitment (termed an Advanced Market-type approach) has been promoted in recent months as a means of accelerating development of HIV or malaria vaccines, which are essentially in the design/early development-stage;
- A wide variety of concerns have been raised regarding proposals for the Advanced Market-type APCs and many of these need further study, as the concept of 'due diligence' would require of potential sponsors of any APC;
- Beside the AM-type APC there exist a variety of other approaches to advance purchase commitments which would probably be easier to implement with existing or late development-stage vaccines because there is much greater certainty surrounding the products to which they could be applied;
- Advanced purchase commitments would ideally overcome two problems with commercial engagement in vaccines for developing countries: firstly, reluctance to engage in new product development specifically for developing countries; and secondly, conservative sizing of manufacturing capacity which occurs when a product is developed initially for more affluent markets, but which means that early supply and price for poorer developing countries are constraints;
- Measures to build confidence among commercial players in future revenues from vaccines (and hopefully increase their engagement in development/supply of vaccines for developing countries) would have greatest credibility if they start with the products that already exist;
- Public sector capacities in vaccine demand/uptake projection and procurement practices are historically regarded as unreliable, not subject to performance comparisons, and generally in need of strengthening and reshaping;
- GAVI and the Vaccine Fund have received pledges of increased funding that could be used for long-term supply contracts for existing products and infrastructure strengthening but total funding is still below the desirable level. The International Finance Facility for Immunization is urgently needed;
- For certain categories of recent products that are already proven to be capable of reducing disease burdens in developing countries (rotavirus, pneumococcal, and new combination vaccines), there will exist over the next few years a narrow window-of-opportunity to test (in a competitive environment) whether advance purchase commitments can influence manufacturers supply capacity and pricing decisions;
- Buying recent products at reasonable prices will not only increase vaccine producers confidence in future markets but will provide immediate revenues from which they can fund more R&D;

- A mix of different interventions *at each stage*, tailored to the different phases of vaccine development and introduction, will be needed to move the relevant candidates/products through the progression in an optimal manner. Support for overall 'system strengthening' is also essential;
- The specific utility of different forms of advanced purchase commitments and the priority for other forms of interventions and support need to be examined in this context.

2. Advanced purchase commitments

As of the time of writing it is clear that a variety of types of advanced purchase commitment exist and further work is necessary to define which are most appropriate for different categories of product. Included in this bigger picture is the need to resolve disagreements around the Center for Global Development proposal for the Advanced Markets-type of approach for early stage vaccines.

It should be recognised that most of those who have raised concerns on the Advanced Markets idea do not question the usefulness of demonstrating a market 'pull' to engage industry, or the likely feasibility of advanced purchase commitments for existing or even late stage products. Their concerns are largely whether an experimental mechanism such as the Advanced Markets proposal is feasible, appropriate for early stage vaccines where there is great uncertainty as to the likely product, and likely to have the desired impact on commercial investment decisions.

It is **recommended** that:

An impartial 'blue ribbon' panel of economists, experts in vaccine development, and commercial pharmaceutical investors should be charged with recommending, within six months, how to proceed.

Key questions the group should examine include:

- What forms of advanced purchase commitments are potentially useful and feasible in engaging commercial vaccine development resources on products for developing countries and in what form for vaccines at different stages of development?
- What other instruments and forms of support should be given priority taking into account the development-stage of important vaccines for developing countries and the needs to strengthen the overall vaccine development and introduction system?
- Where could advanced purchase commitments potentially be most useful in encouraging the appropriate sizing of manufacturing plant capacity to meet rapid vaccine introduction needs in developing countries?
- To which institutions should responsibility be assigned for implementing those arrangements that are deemed potentially the most useful?

As described below there are, in fact, a number of ways in which credible 'pull' or advanced purchase commitments could be explored to address immediate needs and gain experience.

3. Matching instrument and financial support to product development stage, system strengthening needs and other opportunities to use vaccination to address diseases associated with poverty.

Juxtaposing the various categories of vaccines (design/early development-stage, late development-stage, 'recent', 'underused') against the steps in the vaccine development and

introduction process (Figure 1) suggests that different interventions (or more likely **a mix of different interventions**) will be needed **at each stage** to move the relevant candidates through the progression in an optimal manner. These probably will include:

- 'Push' interventions, to accelerate candidate product design/development by engaging many players;
- 'Pull' interventions, that variously provide economic reward and assure product use, both directly through purchase and indirectly by establishing the delivery systems that mean products can reach maximum number of recipients;
- Product development partnerships, i.e., brokers to expedite the passage of candidate products down the development and introduction pathway, as this needs many linkages; and
- Support for system strengthening as a whole (as described in the Background section, C.1.).

This conclusion is reinforced if one considers the wider 'system' capacities that are needed. Financial reward should be assured for commercial players but even significant rewards would not overcome the problems and delays that are caused by lack of capacities that only the public sector could or should provide, such as regulatory guidance or comparative testing.

The conclusion is further reinforced by the fact that in the future vaccine development and supply for developing countries may not be solely a function of the activity of the traditional major companies but is likely to involve a greater role by new players such as applied research institutes (e.g., IVI), not-for profit product development partnerships, biotechs, and developing country manufacturers. These will require cost sharing on a pay-as you-go basis as they cannot generally mobilise major resources from revenues on other products as can large pharmaceutical companies.

Table 7 shows the present and future opportunities for alleviating diseases associated with poverty through vaccination, i.e., both by applying existing vaccines and accelerating the development and introduction of new vaccines.

It suggests a strategy to consider advance purchase commitments for HIV and malaria vaccines based on the experience that will come from developing advanced purchase commitments successively for: (i) existing under-used vaccines; (ii) 'recent' new vaccines; (iii) late development stage vaccines and ultimately (iv) early development stage vaccines (if judged feasible and useful).

It is **recommended** that any pledge to develop advanced purchase commitments for a range of existing and future products should be accompanied by agreement, through the 'blue ribbon panel' discussed above to rapidly establish priorities for the other 'push' and 'system' strengthening interventions that need to be in place.

A comprehensive approach will give confidence to all the necessary players, including major commercial companies, that the commitment to vaccination against the diseases associated with poverty is broad and will last long beyond the upcoming G7/8 round.

**Table 7: Accelerating vaccination for control of diseases associated with poverty:
Location of major challenges and current needs**

Vaccine category	Disease/vaccine examples	Vaccine design or development issues	Use policy issues	Supply/procurement/ issues	Delivery system issues	Current major needs		Comments
						Candidate product related	'System' related	
Under-used	DTP Measles Hepatitis B Rubella	None	None (except for Rubella strategy safety)	Adequate, competitive global supply capacity exists	Lower reach (sometimes <50%) to poorest/rural infants in developing countries	Adequate funding for multi-year supply contracts, split among low cost suppliers to maintain competition	Better demand estimates Funding to strengthen delivery 'infrastructure' and other DEC capacities e.g., for trials and regulation	Polio eradication should be completed. Complete implementation in 2-5 years
'Recent'	Hib New combinations e.g., DTP+, others Rotavirus Pneumococcal	None (competition anticipated where currently sole suppliers)	For some vaccines disease burden studies and cost-effectiveness analysis needed	Production technologies well known: supply capacity likely to be adequate if market demonstrated	Lower reach (sometimes <50%) to poorest/rural infants in developing countries	Funding for multi-year supply contracts, split among lower cost suppliers to encourage competition Policy guidelines for newest	As above. Policy for higher prices for initial purchase for poorer countries to encourage new scale manufacturing Learning from APCs for 'under-used' vaccines	Over next 0-10 years
Late development stage	Meningococcal A Dengue Alternative pneumococcal HPV New combinations	Design issues mostly known Pneumococcal options desirable (easier production, cheaper), if feasible	Mostly known	Production technologies known and can be scaled for sufficient supply	As above	'Push' support to clinical trials Support to PDPs and ADIPs Anticipation of required utility studies for policy formulation	As above Projections of uptake/demand Learning from APCs for 'recent' vaccines	Over 0-15 years

(Continued)

**Table 7: Accelerating vaccination for control of diseases associated with poverty:
Location of major challenges and current needs**

Vaccine category	Disease/vaccine examples	Vaccine design or development issues	Use policy issues	Supply/procurement/ issues	Delivery system issues	Current major needs		Comments
						Candidate product related	'System' related	
Early development or 'design' stage	HIV/AIDS Malaria Tuberculosis Leishmaniasis	Information needed to design more effective candidate products, but difficult/costly to generate	Mostly difficult to anticipate absent knowledge of vaccine design; some safety questions for malaria, possibly others	Difficult to foresee, beyond those historically known for existing or late stage products	As above. For HIV vaccines: delivery system to adolescents/adults in poorer countries needs creating	Support to applied research; translational research; pilot lot production; assays, standards, definition of trial end-points etc for comparisons. Support to PDPs and other 'Push' instruments	As above Learning from APCs for under-used, recent and late stage vaccines Planning for adolescent and adult delivery system	Some actions needed now but timeframe for completion is uncertain

DRAFT 24/02/05

Research Study: Key Stakeholders and Funding for HIV and Malaria Vaccine R&D

Terms of Reference

1. Background

In November 2004, the Chancellor announced that the UK was willing to work with partners to develop and enter into Advance Purchase Commitments (APCs) for malaria vaccines. Further announcements indicated that the UK will explore opportunities to enter into similar commitments for HIV vaccines.

The UK Department for International Development (DFID) is now leading work with other Government departments to develop and consult on proposals for APCs.

APCs are one means that can be used as part of a package of instruments to accelerate the development and use of priority vaccines for use by developing countries. Other means include direct investment in research and development (R&D) activities and incentives, such as tax credits, to increase private sector participation in R&D efforts. The role and added value of APCs in relation to other instruments will be important factors informing their design and use.

2. Purpose

To identify current stakeholders, instruments and funding for the development of (i) malaria vaccines, and (ii) HIV vaccines.

3. Objectives

The study will have the following objectives for both malaria and HIV vaccines:

- (a) To identify key R&D and manufacturing stakeholders, with a particular focus on applied research and product development activities.³⁵
- (b) To identify current levels of private and public funding and expenditure on vaccine R&D.
- (c) To identify existing incentives and other instruments supporting vaccine R&D and which could support future introduction (e.g. GAVI)?
- (d) To summarise current strengths and weaknesses in the vaccine development and introduction pathway.
- (e) To briefly discuss the implications of (a) – (d) for the design of advance purchase commitments.

4. Methodology

Desk review and with key informant interviews.

³⁵ The focus of the study is on R&D focused on developing products for use in developing countries. Detail on basic and primarily academic research is not required.

5. Outputs

A short research report setting out findings with a short commentary on the implications for Advance Purchase Commitments.

DFID will be responsible for any printing and dissemination of the report.

6. Time

Up to 5 days consultancy to be completed by 31 March 2005.

7. Management

DFID will issue a consultancy contract to be managed by Saul Walker (Policy Division).

Designers or manufacturers of HIV/AIDS vaccine candidate products in clinical trials

(Suggestions for additions welcomed)

	Number
Advanced Bio Sciences Laboratories (ABL)	
Australian-Thai Vaccine Consortium	
AVANT Immunotherapeutics, Inc.	
Aventis Pasteur (now Sanofi Pasteur)	
Baxter HealthCare Corporation, Hyland Immuno Division	
Biovector SA	
Bristol-Meyers Squibb/Oncogene	
British Biotech PLC	
Cel-Sci	
Chiron	
Chiron/Biocine	
CIGB	
Cobra Pharmaceuticals	
Epimmune	
FIT Biotech	
Genentech Inc.	
Genentech Inc./VaxGen	
GenVec	
GlaxoSmithKline	
Impfstoffwerk Dessau – Tomau GmbH (IDT)	
Merck	
MicroGeneSys Inc.	
SmithKline Beecham Biologicals (now GSK Biologicals)	
St Jude Children's Research Hospital	
Therion Biologicals Corp.	
UBI	
University of Massachusetts Medical School (UMMS)	
VaxGen	
Vical Inc.	
Wyeth	
Wyeth-Lederle	

Source: International AIDS Vaccine Initiative database of HIV/AIDS vaccines in human/clinical trials; <http://www.iavireport.org/trialsdb/> accessed 30 March 2005

NB: This listing includes only designers or producers of vaccine candidate products thought to be in or about to enter clinical trials in 2005. The list of products in preclinical research/testing is considerably longer.

Designers or manufacturers of malaria vaccine candidate products in clinical trials:

(Suggestions for additions welcomed)

Bharat Biotech International, India
CSL Ltd, Melbourne, Australia
CSIRO, Melbourne, Australia
Dictagene, Lausanne, Switzerland
GlaxoSmithKline Biologicals, Belgium
GroPep Ltd, Adelaide, Australia
Impfsoffwerke Dessau-Toran (IDT), Germany
International Center for Genetic Engineering and Biotechnology, India
Institut Pasteur, Paris, France
La Trobe University, Melbourne, Australia
Naval Medical Research Center, Dodd, USA
Oxon Pharmacies/Oxxon Therapeutics, Oxford, UK
Queensland Institute of Medical Research, Australia
Royal Brisbane Hospital, Australia
Staten Serum Institute, Denmark
University of Lausanne, Switzerland
University of Oxford, UK
Walter Reed Army Institute of Research (WRAIR), DoD, USA
WRAIR Pilot Lot Production Facility, Forest Glen, MD, USA

Sources: European Malaria Vaccine Initiative Annual Report 2004; Malaria Vaccine Initiative Website www.malariavaccine.org/ab-current_projects.htm , accessed 11 March 2005; WHO database Portfolio of malaria vaccine candidates currently in development – October 2004, http://www.who.int/vaccine_research/documents/en/malaria_table.pdf accessed on 30 March 2005.

NB: This listing includes only designers or producers of vaccine candidate products thought to be in or about to enter clinical trials in 2005. The list of products in preclinical research/testing is considerably longer.

Facilities available for production of pilot lots for clinical testing

(Suggestions for additions welcomed)

See also the report '*Speeding the manufacture of an HIV vaccine: Policy issues and options*'. International AIDS Vaccine Initiative, 2005. 18pp.

Public sector

USA

WRAIR Forest Glen, MD, USA
Groups contracted by NIH/NIAID

UK

National Bio-manufacturing Centre, Liverpool – planned to open early 2006

Commercial

See IAVI report referred to above and WHO survey by the Department of Vaccines and Biologicals, around 2003

Organizations conducting or evaluating clinical trials capacity strengthening in disease endemic counties, particularly sub-Saharan Africa

(Suggestions for additions welcomed)

Public sector/Not-for-Profit

Based in disease endemic countries

African Malaria Network Trust (AMANET)

India/ICMR

Industrialized country based

European Developing Country Clinical Trials Program, EC
NIH/NIAID, USA
Australia, for Papua New Guinea

Aeras Global Tuberculosis Vaccine Foundation
EMVI
IAVI
IPM
MVI/Voxiva

International

Special Programme for Research and Training in Tropical Diseases (TDR)

Commercial

Quintiles International

Strengths, current challenges, and potential bottlenecks in HIV vaccine development and introduction

It is proposed that the current and potential future challenges for HIV vaccine development and introduction be arrayed in the format below to facilitate development of consensus on the capacities of the overall vaccine development and introduction system that need strengthening or increased resources.

Sources for this process include but are not limited to:

- The consultation for the Global HIV Vaccine Enterprise scientific plan - (<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=544553>)
- AIDS vaccines for the world: Preparing now to assure access, IAVI, 2000
- A new access paradigm: Public sector actions to assure swift global access to AIDS vaccines, IAVI, 2001
- Demand estimates study by WHO/UNAIDS/IAVI
- Manufacturing report, IAVI, 2005

Table A.6.1. Strengths, current challenges, and potential bottlenecks in HIV vaccine development and introduction

Step	Strengths	Current challenges	Potential bottlenecks
Basic research			
Applied research			
Translational research			
Preclinical research			
Production process development			
Clinical research: Phase I			
Clinical research: Phase II			
Clinical research: Phase III			
Regulatory assessment			
Manufacturing			
'Utility' studies			
International policy guidelines			
National policy formulation			
Resource mobilization			
'Procurement'			
Implementation			
Pharmaco-vigilance			

Strengths, current challenges, and potential bottlenecks in malaria vaccine development and introduction

It is proposed that the challenges for malaria vaccine development and introduction be arrayed in the format below to facilitate development of consensus on the capacities of the overall vaccine development and introduction system that need strengthening or increased resources.

Sources for this process include but are not limited to:

- Malaria Vaccine Technology Roadmap exercise details of which can be found at (<http://www.malariavaccineroadmap.net/roadmap.html>)
- Malaria vaccine demand estimates study, MVI/Boston Consulting Group, 2005
- EMVI Annual Report - 2004

Table A.6.1. Strengths, current challenges, and potential bottlenecks in malaria vaccine development and introduction

Step	Strengths	Current challenges	Potential bottlenecks
Basic research			
Applied research			
Translational research			
Preclinical research			
Production process development			
Clinical research: Phase I			
Clinical research: Phase II			
Clinical research: Phase III			
Regulatory assessment			
Manufacturing			
'Utility' studies			
International policy guidelines			
National policy formulation			
Resource mobilization			
'Procurement'			
Implementation			
Pharmaco-vigilance			

Persons contacted in preparation of the report

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Laura Efros, Merck Vaccines, USA

Sarah Ewart, Malaria Vaccine Initiative, PATH, Seattle, USA

Andrew Farlow, Department of Economics, Oxford University

Tore Godal, former Executive Secretary, GAVI, and former Director, Special Programme for Research and Training in Tropical Diseases, Geneva

Marie-Paul Kieny, IVR, WHO, Geneva

Jenny Lanjouw, University of California at Berkley, CA, USA

Orin Levine, PneumoVaccine Accelerated Development and Introduction Program, USA

Ruth Levine, Center for Global Development, Washington, DC, USA

Don Light, Princeton University

Julian Lob-Levyt, Executive Secretary, GAVI/Vaccine Fund

Richard Mahoney, formerly International Vaccine Institute, Seoul, S. Korea

Zarifah Hussein Reed, TDR/IVR, WHO

Jane Rowley, International AIDS Vaccine Initiative

David Salisbury, Principal Health Officer (Immunization), Department of Health, UK

Adrian Towse, Office of Health Economics, London

John Wecker, Rotavirus Vaccine Program, PATH

About the author: Roy Widdus, Ph.D.

The author has academic training in biochemistry, microbiology, and infectious disease epidemiology. Early in his career, he worked in industrial microbiology research and commercial drug design.

He has been involved in a wide range of activities relating to vaccine policy analysis and infectious disease control. These include:

- Project director, US National Academy of Sciences' Institute of Medicine studies on: Priorities for Accelerated Vaccine Development; and Vaccine Supply and Innovation. (These in part formed the basis for creating the US National Vaccine Program Office and the US National Vaccine Injury Compensation Program (1982 -1987).
- Programme Coordinator, in the senior management team of the World Health Organization's Global Programme on AIDS, 1988-1991;
- Executive Director, US National Commission on AIDS (1992-1993).
- Consultant and Interim Director of the US National Vaccine Program Office, authoring the first US National Vaccine Plan (1993-1995).
- Coordinator, Children's Vaccine Initiative, Geneva (1995 – 1999); (CVI was the predecessor to the Global Alliance for Vaccines and Immunization).

From 2000 to early 2005, he managed the Initiative on Public-Private Partnerships for Health, under the Global Forum for Health Research in Geneva. The Initiative focused on collaborations addressing development and access to new drugs, vaccines and diagnostics to combat diseases associated with poverty.

He now undertakes consulting assignments on product development and introduction, to improve control of the major infectious diseases in developing countries that result in serious health inequities for the poor.