

Executive Summary

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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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 as far as the author is aware not instituted by UNICEF until 2004 because funds provided for international procurement 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.

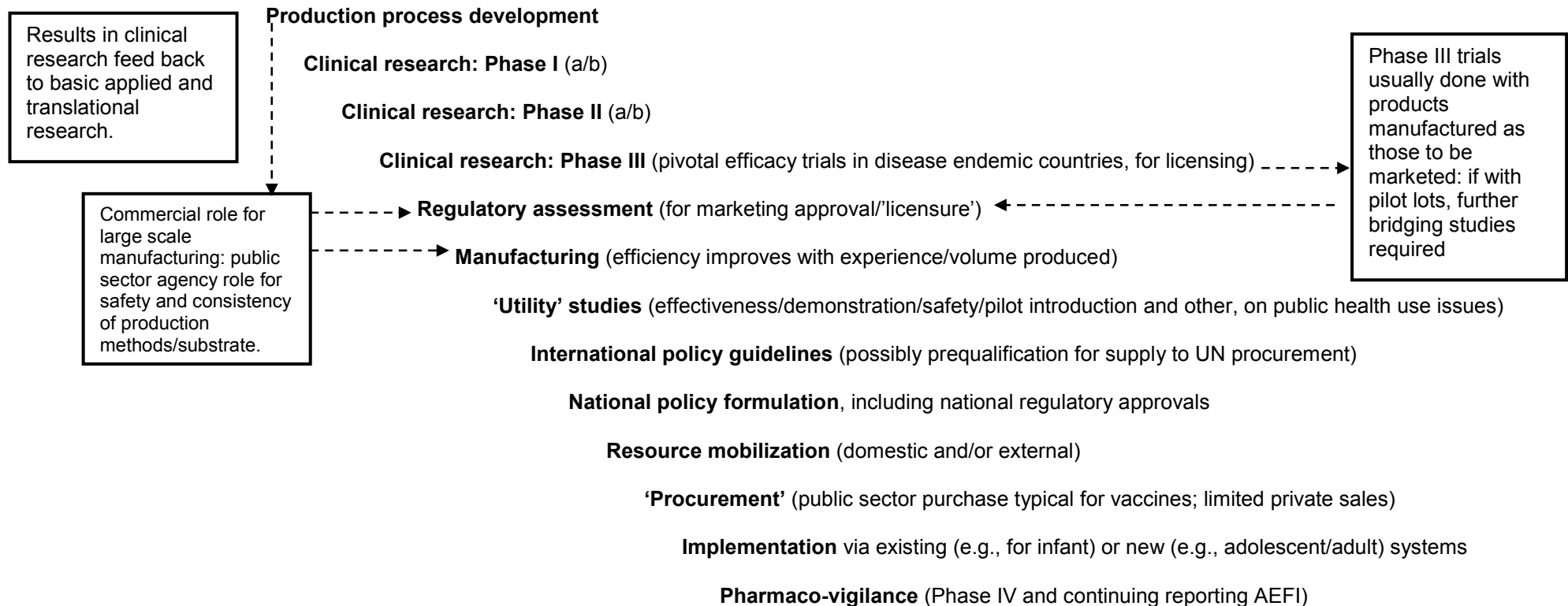
Figure S.1: Steps in vaccine development and introduction into poorer countries

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

