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Assessing the global needs for vaccine research and development

Results of a Joint GAVI/WHO meeting, Geneva, 4-5 November 1999

GAVI Global Alliance for Vaccines and Immunization

DEPARTMENT OF VACCINES AND BIOLOGICALS

World Health Organization
Geneva

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Glossary

AFRIMS	Armed Forces Medical Research Institute
CEO	chief executive officer
CRO	contract research organization
CVD	Center for Vaccine Development
CVD–Chile	Centro para Vacunas en Desarrollo, Chile
CVP	Gates Children's Vaccine Program
DALYs	disability-adjusted life years
DOD	Department of Defense (USA)
EPI	Expanded Programme on Immunization
ETEC	enterotoxic *Escherichia coli*
GAVI	Global Alliance for Vaccines and Immunization
GCP	good clinical practice
GDP	gross domestic product
GFVC	Global Fund for Children's Vaccines
GMP	good manufacturing practice
IAVI	International AIDS Vaccine Initiative
ICC	Interagency Coordination Committee
ICDDR,B	International Center for Diarrheal Diseases Research, Bangladesh
IVI	International Vaccine Institute, Korea
NMRI	Naval Medical Research Institute
NAMRU	Naval Medical Research Unit (USA)
NFP	not-for-profit company
NIAID	National Institute of Allergy and Infectious Diseases (USA)
NIDs	national immunization days
NMRI	Naval Medical Research Institute (USA)
PATH	Programme for Appropriate Technology in Health
PEI	Polio Eradication Initiative
QALYs	quality-adjusted life years
RSV	respiratory syncytial virus
TDR	Special Programme for Research and Training in Tropical Diseases (WHO)
UNDP	United Nations Development Programme
WEF	World Economic Forum
WRAIR	Walter Reed Army Institute of Research
VTC	vaccine trial centre
YPLLs	years of potential life lost

Summary and items for action

Recognizing that "Accelerating the research and development efforts for vaccines and related products specifically needed by developing countries, particularly vaccines against HIV/AIDS, malaria and tuberculosis" is one of the fundamental objectives of the Global Alliance for Vaccines and Immunization, the purpose of this "pre-Task Force" on Research and Development meeting was to:

- Define the type of vaccines, in addition to AIDS, malaria and tuberculosis, that should be targeted by GAVI and prioritized for development;
- Identify the gaps that exist globally which are preventing these vaccines from being developed or are delaying their development;
- Prepare a preliminary broad strategy to begin to address the gaps and find solutions.

Items for action

- GAVI should foster research and development of developing-market vaccines against diseases for which the burden is largely limited to the developing countries.
- A Task Force on Research and Development should be established to join the other three task forces that assist the GAVI Secretariat and Working Group in achieving GAVI's objectives.
- The GAVI Task Force on Research and Development should work with WHO, epidemiologists from developing countries, industry, UNICEF, the World Bank and other partners to set the priorities for which developing-market vaccines, in addition to those for HIV, malaria and tuberculosis, are most needed.
- Where epidemiologic, microbiologic or parasitologic data are deemed to be insufficient to allow a fair assessment of disease burden, the collection of those data should be undertaken.
- A GAVI Task Force on Research and Development should "push" the development of these vaccines by:
  - fostering partnerships with industry;
  - assisting in obtaining patent protection;
  - facilitating access to pilot-lot formulations (through various mechanisms);
  - facilitating sponsorship (i.e. financial support) for clinical trials;
  - exploring ways to make clinical trials simpler and more economical.

- The global capacity for production of pilot-lot formulations of different types of vaccine under GLP and good manufacturing practice (GMP) should be catalogued (and periodically updated).
- The Task Force on Research and Development should, in collaboration with the United States National Institute of Allergy and Infectious Diseases (NIAID), review future issues of the Jordan Report to ensure that research progress on the GAVI priority vaccines is contained therein.
- The GAVI Task Force on Research and Development should oversee the preparation of a catalogue of clinical trials facilities in industrialized and developing countries with experience or potential for evaluating developing-market vaccines in Phase I–IV clinical trials. (This must be annually updated.)
- GAVI should strengthen the clinical trials research units in Africa, Asia, and Latin America that have established track records in performing GCP clinical trials in adult and paediatric populations and should facilitate the establishment of necessary new sites (e.g. for testing tuberculosis vaccines).
- Non-profit companies and "virtual corporation" models are attractive strategies to be pursued for nurturing the development of specific developing-market vaccines.
- More direct forms of academia/industry partnership should also be encouraged.
- The GAVI Task Force on Research and Development should actively explore opportunities in large developing countries such as Brazil, China, India and Indonesia that have large-scale manufacturing capacity and strong research capability.
- The "push" activities of the GAVI Task Force on Research and Development should be coordinated with the "pull" efforts of the GAVI Task Force on

1. Background

The Global Alliance for Vaccines and Immunization (GAVI), a newly formed coalition in which the principal partners include representatives of the developing countries of the world, the World Health Organization, UNICEF, the World Bank, industry, bilateral agencies, the Gates Children's Vaccine Program and the Rockefeller Foundation, has five major objectives:

- Improving access to sustainable immunization services;
- Expanding the use of all existing safe and cost-effective vaccines;
- Accelerating the development and introduction of vaccines;
- Accelerating the research and development efforts for vaccines and related products specifically needed by developing countries, particularly vaccines against HIV/AIDS, malaria and tuberculosis;
- Making immunization coverage a centre-piece in the design and assessment of international development efforts, including deep debt relief.

To begin to address the objective of accelerating the development of vaccines of particular importance for developing countries, a meeting was convened in Geneva on 4–5 November 1999, co-sponsored by GAVI and by the Intercluster Vaccine Research Initiative of the World Health Organization. GAVI's work on this objective is likely to guided by a "GAVI Task Force" in the future. Therefore, this meeting will hereafter be referred to as the "Pre-Task Force" meeting. The purpose of the meeting was to:

- Define the type of vaccines, in addition to those for AIDS, malaria and tuberculosis, that should be targeted by GAVI and prioritized for development;
- Identify the gaps existing globally that prevent these vaccines from being developed or delay their development;
- Prepare a preliminary broad strategy to begin to address the gaps and find solutions.

Vaccine development in the last two decades of the twentieth century

In the last two decades of the twentieth century, extraordinary advances in biotechnology were applied in the area of vaccine development, resulting in the licensure of exciting new vaccines such as *Haemophilus influenzae* type b (Hib) conjugates, acellular pertussis, recombinant hepatitis B and attenuated varicella.

Although most of the basic scientific breakthroughs that made these vaccines possible were generated in public sector (academic and government) research institutions, most of the cost for their clinical development, including the support of extensive phase II and III clinical trials, was borne by the "big pharma" vaccine industry in industrialized countries. An investment of several hundred million dollars was typically required to bring each of these new vaccines to licensure. For this reason, within the first few years after licensure and commercialization of those products, their unit price remained high, as companies sought to recoup their large investments through sales in markets in wealthy, industrialized countries. In recent years, the need to assure a return on investment and avoidance of risk has influenced the decisions made by industry with respect to investment in research and development for future products.

2. Prioritizing vaccines for accelerated research and development

2.1 Vaccines for which research and development activities are falling behind

Vaccines for which research and development are falling behind can be conveniently divided into two main categories, "impeded" vaccines and "developing market" vaccines.

2.1.1 Vaccines suffering from non-economic bottlenecks ("impeded" vaccines)

These are candidate vaccines that would almost certainly have substantial markets in industrialized countries but certain scientific, ethical or public-perception obstacles dissuade the vaccine industry from making investment in their development a high priority. For example, the fear that M protein-based vaccines against Group A *Streptococcus pyogenes* and vaccines against respiratory syncytial virus (RSV) might elicit serious adverse reactions has stifled the pace of their development, despite the likelihood of large markets for these vaccines in industrialized countries.

2.1.2 Vaccines lacking substantial markets in industrialized countries but offering potential markets in developing countries ("developing market" vaccines)

There are a number of diseases for which the burden is prominent in developing country populations but little if any risk is posed for individuals in industrialized countries unless they travel to developing areas. Certain bacterial diseases (e.g. *Shigella* and enterotoxic *Escherichia coli* infections, cholera, typhoid fever and group A meningococcal infections), viral diseases (e.g. dengue fever, hepatitis E) and parasitic infections (e.g. malaria, leishmaniasis and schistosomiasis) provide examples. The fact that markets in industrialized countries are either lacking or limited to travellers has heretofore provided little incentive for industry to make the large investments necessary to finance the clinical development of these vaccines. Henceforth, for reasons of brevity, such vaccines will be referred to as "developing market" vaccines. This term will reflect the fact that these vaccines are particularly targeted for use in developing countries and will also convey the notion that non-traditional markets will have to be developed for these vaccines in those countries. For example, whereas in industrialized country markets industry may rely on a low volume/high margin approach, the profitability of "developing market" vaccines in less-developed countries will probably require adoption of a high volume/low margin approach.

2.2 Defining the vaccines of interest to the research and development component of GAVI

It was agreed that, at least initially, a GAVI Task Force on Research and Development should focus its efforts on fostering the development of "developing market" vaccines critically needed by developing countries.

2.3 Prioritizing specific vaccine projects in which GAVI should be involved

GAVI's involvement in championing the development of vaccines against AIDS, malaria and tuberculosis is specifically instructed in its charter. Deciding what developing-market vaccines should draw the additional focus of GAVI will depend on consideration of a number of factors, including:

- The magnitude of the disease burden;
- The public perception of the disease and of the need for its control;
- Whether the science is sufficiently mature to generate rational vaccine candidates;
- Whether vaccine candidates are already in clinical trials or are approaching being ready for transition to clinical trials;
- Microbiological/parasitological factors (e.g. whether multiple serotypes or antigens from different stages of the parasite must be included in the vaccine);
- Whether alternative public health control measures are available;
- Whether an effective treatment exists;
- Whether the disease has the potential to cause epidemics and pandemics;
- Whether a travellers market exists for the vaccine in industrialized countries;
- Whether the vaccine can be combined or concomitantly delivered with other vaccines through existing immunization services;
- Whether the vaccine has characteristics that are particularly attractive for use in developing countries such as non-parenteral (e.g. mucosal or transcutaneous) administration, an immunization schedule that requires only 1–2 doses and effectiveness in infants;
- Estimates of the cost-effectiveness of the vaccine, assuming optimal implementation.

To obtain preliminary information in an informal manner, the participants were asked to respond to a questionnaire asking them to rank vaccine development priorities for bacterial, viral and parasitic developing market vaccines, taking into consideration the above criteria. The results of this informal survey are summarized in Table 1. It was agreed that during the next year, in collaboration with the WHO Intercluster Vaccine Research Initiative, a GAVI Task Force on Research and Development must undertake a detailed, systematic analysis to select a few initial priority vaccines to be fostered, in addition to vaccines for AIDS, malaria and tuberculosis, taking into consideration all of the above-mentioned criteria.

3. Identifying specific gaps for research and development of developing-market vaccines

The GAVI Pre-Task Force focused on identifying the gaps and barriers faced by relevant current vaccine development programmes. It is anticipated that this information can allow strategies to be devised to remove the hurdles, thereby accelerating the vaccine development programmes.

3.1 Availability of disease-burden data

Disease burden may be quantified with respect to morbidity, mortality, or certain epidemiologic currencies such as disability-adjusted life years (DALYs), quality-adjusted life years (QALYs) or years of potential life lost (YPLLs). It was generally acknowledged that large gaps exist in the quality of disease-burden data.

3.1.1 Burden of Shigella disease as model

A recent publication, K Kotloff et al., (*1*) describing in detail an exercise to estimate the global burden of diarrhoeal disease and dysentery caused by *Shigella*, was used to illustrate the complexities, limitations and advantages of such an exercise. This was deemed to be a particularly useful example because the main clinical syndromes caused by *Shigella*, diarrhoeal disease and dysentery, are also caused by a number of other enteric pathogens. Moreover, it is an antigenically diverse pathogen, as there are four species and 37 serotypes and sub-types of *Shigella*. Therefore, adequate microbiologic as well as epidemiologic data are needed to estimate the global disease burden of *Shigella*. The burden of *Shigella* infections was calculated separately for developing versus industrialized countries. In this comprehensive exercise, the global burden was calculated with respect to deaths, severe cases (requiring hospitalization), moderate cases (seen as outpatients in treatment centres) and mild cases (that do not seek health care). Since both the incidence of *Shigella* disease and mortality disproportionately affect certain age groups, the burden was calculated separately for relevant age strata: < 1 year, 1-4 years, 5–14 years, 15–59 years, and ≥60 years of age. Serogroup and serotype data needed to direct vaccine development strategies were analysed in relation to different geographic areas. Finally, a sensitivity analysis was performed to estimate the high and low range of cases and deaths. A summary of the global burden of *Shigella*, with low and high estimates, is shown in Table 2.

The exercise of estimating the global burden of *Shigella* revealed several factors relevant to assessing the burden of several other diseases of interest to GAVI. The first was the surprising paucity of available data on the incidence of diarrhoeal

disease among adults in developing countries. Whereas prospective paediatric cohort studies in multiple sites in the developing world have documented the number of episodes of diarrhoeal disease per child per year in infants, toddlers and pre-school children, analogous data for adults simply do not exist. Another revelation was the dearth of epidemiologic and bacteriologic data from Africa, in contrast with Asia and Latin America. Finally, it was noted that many of the centres of excellence in Asia and Latin America, where clinical trials of various vaccines have been carried out during the past two decades, are also sites where the most comprehensive epidemiologic and microbiologic data on diarrhoeal disease were generated. These sites include the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B) and the Centro para Vacunas en Desarrollo, Chile (CVD-Chile).

3.1.2 Institute of Medicine model

A model in which QALYs were used as a common epidemiologic currency was presented as an implement to guide the setting of vaccine development priorities. This model was recently utilized by the Institute of Medicine as a proposed tool for decision-making. When utilized to assess the vaccine needs for the United States, and considering possible therapeutic as well as preventive uses of vaccines, four levels of vaccine priorities were established which reflected differences in cost/QALY saved. The details of this model and the vaccines identified in each of these categories can be found at www2.nas.edu/hpdp/.

3.1.3 Disease burden in perspective

Despite the paucity of precise burden data for many diseases, it was agreed that the precision required will depend on how the data are to be used. Arguably, even the currently available imprecise disease-burden estimates can allow a preliminary setting of priority among competing vaccine projects, since other equally important factors besides disease burden must be considered. However, the general need to improve both epidemiologic and microbiologic surveillance in sub-Saharan Africa was noted. Representatives of the private sector remarked that for them estimates of the global and regional burdens of disease were important to establish priorities internally, and would influence whether they would collaborate with GAVI in pushing the development of certain developing-market vaccines. It was generally agreed that, at least for tuberculosis, malaria and HIV/AIDS, current disease-burden data were sufficient to validate their high priority as a focus for GAVI. Diarrhoeal diseases, acute lower respiratory infections and parasitic infections have been recognized as important public health targets for intervention. For diarrhoeal diseases, adequate data exist from studies in developing countries to incriminate the most important pathogens. Data to attribute bacterial and vial etiologies to lower respiratory infections are more tenuous because of the difficulty in obtaining relevant clinical specimens for microbiologic analysis. Indeed, experience with Hib conjugate vaccine in Chile and the Gambia suggests that vaccine probe studies that measure the difference in hospitalization rates versus controls for pneumonia in vaccinated infants provide the most accurate (as well as relevant) measure of specific disease burden. For parasitic diseases other than malaria the quality of the data varies by geographic region and by infection. Thus, there is a need for well-designed systematic surveys to generate more precise burden data.

3.2 Global monitoring of the status of vaccine development

General information about the status of existing and the prospects for new vaccine research programmes globally is made available in a form suitable for the educated lay public in the WHO publication *State of the world's vaccines and immunization*. An updated version is being prepared for publication in the year 2000. This monograph provides a useful "broad brush" review that promotes public support for vaccine programmes.

Detailed information on vaccine research is provided in the annual Jordan Report prepared by the staff at the National Institute of Allergy and Infectious Diseases (NIAID), USA. This was considered by all participants to be a "model publication". However, there was some concern that the Jordan Report might be incomplete, particularly with respect to research activities in developing countries. It was agreed that several experts identified by GAVI will review the Jordan Report for potential gaps. A Jordan Report supplemented in this manner could serve the broader global audience that GAVI must target.

3.3 Access to pilot-lot formulations

Participants agreed that there are two broad classes of pilot-lot formulations. One is adequate for undertaking proof of principle Phase I and early Phase II studies to establish the safety and immunogenicity of the vaccine candidate. Such formulations may not be readily amenable to subsequent scale-up. The other encompasses more sophisticated formulations prepared with considerable forethought as to possible subsequent scale-up to prepare large lots for a Phase III trial and eventual consistent large-scale manufacture.

3.3.1 Regulatory issues relevant to pilot lots

The regulatory requirements and guiding principles for pilot-lot production from the perspective of the US Food and Drug Administration (FDA) were presented as a general approach of regulatory agencies. The regulations require that biological products manufactured for human use, including material for clinical trials, be manufactured in accordance with the current recommendations for good manufacturing practices (GMPs). However, regulatory agencies recognize that it may not be possible to meet full GMPs when manufacturing preparations for early small (e.g. Phase I) clinical trials. Nevertheless, there should be sufficient controls, oversight and testing in place to assure reproducibility of the process and the safety of the product prepared at a licensed facility. The comparability of early pilot-lot material to subsequent scaled-up formulations produced under stringent GMPs would have to be verified.

3.3.2 How do public sector vaccine research groups and small vaccine biotechnology companies obtain pilot-lot formulations?

Within the United States, a network of pilot-lot facilities that specializes in various platform technologies is supported under contract by the NIAID. Priority is given to HIV and malaria vaccine development. The United States Department of Defense (DOD) also supports production of candidate vaccines primarily through the Walter Reed Army Institute of Research (WRAIR) facility.

Several public sector in-country producers of national vaccines were described. The Nordic Public Health laboratories/institutions were originally established to provide vaccines for national use. Recently, however, increased production costs have made small-scale production unprofitable. The institutes have responded to these changes in different ways including privatization (Sweden); expanding to include export capability (Denmark) or preparing to close (KTL-Finland). Each of these facilities may be available for pilot-lot production assuming, in the case of KTL, that the facility can be maintained. RIVM in the Netherlands produces paediatric vaccines primarily for local use. This facility is a member of the WHO Global Training Network and has a tradition of sharing vaccine development expertise with developing countries. Such expertise is currently being developed in Indonesia and Viet Nam. A new member of this Network, the International Vaccine Institute (IVI) based in Seoul, Korea, is planning to construct a pilot-lot production facility (expected to open in 2002) that will have the capability of making both bacterial and viral vaccines. Planned associated research facilities will include an animal facility and clinical testing capability.

Peptide Therapeutics/Oravax, representing small vaccine biotechnology companies, described their pilot-lot capability as virtual. Products of interest are developed/ licensed and clinical lots of vaccines are produced through partnerships.

3.3.3 How do large industrial vaccine manufacturers provide pilot-lot formulations for lower priority projects?

Descriptions of the capacity and prioritization for pilot-lot production by large vaccine companies echoed a common theme. Namely, there is fierce competition internally within companies to have pilot lots produced of contending candidate vaccine projects. Moreover, depending on the specific vaccine, the costs for production of the pilot formulation may be quite high. In addition to process development, issues such as consistency, stability and strict quality control are incorporated into every pilot lot. Within companies, vaccines with the highest probability of success are given high priority for development, including facilitated access to pilot lots.

3.3.4 How do vaccine research groups in developing countries gain access to pilot lots of their vaccine candidates?

Several illustrative examples were given of pilot-lot capacity in developing countries. The Hong Kong Institute of Biotechnology, a private, non-profit manufacturing and technology centre that has been in operation since 1997, has, under contract, prepared pilot-lot formulations of both malaria and schistosomiasis vaccines under GMP conditions. Facilities in Viet Nam and similar Institutes of Biological Products in several cities in China manufacture Expanded Programme on Immunization vaccines, as well as Hepatitis B, Japanese B encephalitis, and Vi polysaccharide parenteral typhoid vaccines. The National Institute of Hygiene and Epidemiology in Hanoi, Viet Nam, locally produced an inactivated oral cholera vaccine that was evaluated in a large-scale field trial. Special efforts are ongoing to meet GMP standards at that Vietnamese facility as well as to strengthen the capability of national control authorities.

3.3.5 Salient summary points on pilot-lot formulations

This survey of representative groups revealed that:

- The difficulty in obtaining pilot-lot formulations of candidate vaccines is one of the most serious and prevalent obstacles facing public sector (and to a lesser degree private sector) researchers who want to transition their research on developing-market vaccines into the clinical arena where Phase I clinical trials can be initiated.
- Pilot-lot production facilities to make relatively simple formulations under GLP or GMP, of the class adequate for Phase I proof of principle trials, exist worldwide.
- Access to pilot lot facilities comes with certain constraints and at high cost.
- Pilot-lot production is costly due in large part to the regulatory standards for use of biologic products in humans.
- Although many facilities are available worldwide, all have competing priorities.
- Whereas there are a few full-service facilities, most units are limited to a few platform technologies. For unique or complex vaccines, there is often a paucity of people trained in this specialized science.
- There is a pressing global need for more bio-engineers skilled both in the ability to prepare high quality pilot-lot formulations and to guide scale-up.
- One of the best models for priority product development is to partner with industry at a point when sufficient information is available to argue credibly for the probable success of the vaccine candidate.

3.3.6 Successful precedent

The four developing-market vaccines (two typhoid and two cholera) which have become licensed products in the last 15 years were the result of public–private partnerships. The public sector incurred most of the costs for the Phase I–III clinical trials, whereas the industrial partners provided formulations of the vaccine for the critical clinical trials. Without these partnerships, these vaccines would not have become licensed products and public health tools, or the pace of their development would have been much slower.

3.4 Clinical trials

3.4.1 Good clinical practice guidelines

The harmonization and codification of good clinical practice guidelines is a major advance that provides a framework for clinical trials to be comparably performed globally. However, in practice, the question of balance was raised with respect to the amount of clinical data to be collected during clinical trials and its documentation. Globally, one sees two broad approaches to performing clinical trials, with respect to the amount of data collected and the monitoring of the data. In general, nowadays, when industry undertakes Phase II clinical trials, an inordinate amount of clinical data is often collected. An evaluation of the types of information requested for critical path (for licensure) Phase II clinical studies sponsored by industry suggested

that up to 80% of the time spent by clinical trial nurses is devoted to investigating and recording adverse events (e.g. common cold) that are not relevant to the vaccine, and concomitant medications. Clinical and laboratory data collected during a Phase II trial must be monitored, and statistically analysed. Industry typically hires contract research organizations (CROs) to monitor and audit the data. Indeed, within the past decade, CROs have themselves become an industry. This approach inflates the cost of industry-sponsored Phase II studies. Up to 30% of the costs of the clinical development stage of a vaccine may be spent on monitoring the clinical data. Obviously, industry will aim to recoup these costs.

By necessity, a different approach is followed by experienced public sector investigators who, while also adhering to GCP guidelines, perform similar Phase II clinical trials at a fraction of the expense. This is accomplished by carefully limiting the collection of data to what is relevant, using simplified case report forms, and by utilizing internal monitoring and auditing. To many investigators who perform clinical trials, it appears that the time has come to undertake a fundamental review to consider how to make clinical trials more rational and economical of information. The concern is not only to achieve balance but also the effect of imbalance (e.g. compromising the recording of relevant data). Inordinate time spent on documenting events of questionable relevance and the collection of data of questionable clinical value greatly adds to the costs of performing clinical trials.

In future, for public/private collaborations in which the public sector will be carrying out the clinical trials, there will have to be agreement beforehand on how the trials are to be conducted. Economy can be achieved if the protocol is designed with attention to avoid unnecessary visits, limiting the collection of data to what is relevant, monitoring of case-report form data by well-trained internal auditors versed in GCP. It was recommended that a GAVI Task Force on Research and Development should convene experienced public sector investigators, representatives of regulatory agencies and heads of departments of clinical research from industry to formalize agreement on ways to simplify and economize clinical trials.

3.4.2 Global infrastructure for vaccine trials

Several examples were given of facilities, sites and networks with clinical trial capability in both industrialized and developing countries. The NIAID, NIH, supports a range of clinical trial networks including those devoted to refinement of Phase I products as well as those capable of doing Phase III efficacy trials. The system is flexible and allows subcontracting to sites with specific populations. In addition to these Vaccine Evaluation Units, NIAID supports the development of several clinical sites in developing countries, although the clinical emphasis is primarily on HIV and malaria. The United States Department of Defense (DoD) has unique clinical trial sites within the DoD setting that allows for clinical capacity which includes sporozoite challenge for malaria vaccine candidates. DoD also supports several foreign sites.

The European Commission assumes no direct responsibility for clinical trial infrastructures in Europe. However, being a major sponsor of vaccine research in Europe, there is a strong interest in this issue, and broad-based consultations on European Union-wide vaccine research and development capabilities have identified a need to strengthen vaccine trial infrastructure. Existing infrastructures, which are

mostly designed for research on specific vaccines and located in countries with long-standing tradition in vaccine development, include a few large centres such as the Oxford Vaccine Group. A recent initiative in Germany is calling for the establishment of a new centre of competence in vaccine research. Enhanced coordination among the various established and emerging European efforts is desirable.

Mahidol University established a Vaccine Trial Center (VTC) in 1986. During the past 13 years, the VTC, which has both inpatient and outpatient facilities, has gained experience in conducting vaccine trials for at least 10 different vaccines, including challenge studies. Most recently, the Thai HIV/AIDS vaccine trial project has required the development of an infrastructure for consensus building, advocacy and bioethics.

The IVI in Seoul, Korea is focusing on the development of an epidemiological and clinical trial network in Asia. In addition to clinical and biostatistical capability, social and economic modelling capabilities are part of this effort. IVI is currently evaluating their ability to coordinate a multi-country trial focused on disease burden using common protocols and methods.

The Medical Research Council Laboratories in the Gambia, West Africa, has been a bastion for the evaluation of candidate vaccines in Phase I–III clinical trials. These have included vaccines against hepatitis B, bacterial meningitis and pneumonia, diarrhoeal disease and malaria.

In South America, the Centro para Vacunas en Desarrollo, Chile (CVD-Chile) has been a leader for years in the performance of Phase I–IV clinical trials of many vaccines. These have included studies of typhoid, cholera, Hib conjugate, pneumococcal conjugate, intranasal influenza vaccines and combination infant vaccines. Follow-up for as long as seven years was maintained in one large-scale trial.

While the global clinical trial capability was found to be generally adequate overall, the absence of developed sites for tuberculosis efficacy studies and the complexity of the study design for those trials was noted.

3.4.3 Overview of sites for clinical trials

Participants in the meeting represent just a fraction of the sites in industrialized and developing countries where the infrastructure and the presence of experienced clinical investigators will allow well-executed clinical trials to be carried out under GCP. The conclusion is that the global capacity for performing clinical trials is presently in good shape, although further strengthening of specific sites will be necessary for specific projects. Table 3 summarizes some of the clinical trial sites in industrialized countries that have a track record for performing clinical trials of developing-market vaccines such as those to prevent malaria, dengue, cholera, typhoid, *Shigella* dysentery and diarrhoea due to enterotoxic *Escherichia coli*. Table 4 summarizes sites in Asia, Africa and Latin America that have a similar track record of performing clinical trials of the same vaccines. Table 5 lists a number of sites in Asia and Africa that are being prepared to undertake clinical trials of developing-market vaccines. It was deemed important to emphasize that substantial financial and human resources must be committed over the next decade to maintain the viability of the current clinical trials sites and to prepare new sites for specific projects.

While the global clinical trial capability was found to be impressive overall, the absence of developed sites for tuberculosis efficacy studies and the complexity of the study design for those trials was noted.

Reference

1. Kotloff K et al. Global burden of *Shigella* infections: implications for vaccine development and implementation of control strategies. *Bull WHO,* 1999, 77:651–666.

4. Addressing the gaps and finding solutions

4.1 GAVI "push" strategies for fostering research and development of developing-market vaccines

The GAVI Task Force on Financing is addressing "pull" mechanisms to encourage industry to invest in the development of developing-market vaccines that would primarily be used in the developing world. Accordingly, the Pre-Task Force on Research and Development concluded that it should address "push" mechanisms by which the public sector, working in conjunction with the private sector, can facilitate the development of developing-market vaccines. Ideally, these pull and push mechanisms would complement one another to synergize the development of developing-market vaccines.

There is a precedent for the success of push mechanisms. The public sector largely financed the development of four developing-market vaccines that became licensed by regulatory agencies in many countries. These vaccines, for which the market in industrialized countries is essentially limited to travellers, include:

- Ty21a live oral typhoid vaccine;
- Vi capsular polysaccharide parenteral typhoid vaccine;
- B subunit/inactivated whole-cell combination cholera vaccine, and;
- CVD 103-HgR live oral cholera vaccine.

4.1.1 Broad strategies for implementing push mechanisms to facilitate and expedite prioritized vaccine development projects

The group concluded that two likely scenarios might result in the accelerated development of priority developing-market vaccines. Both involve public/private partnerships. They include:

- Public sector partnering with "big pharma" in industrialized countries;
- Public sector partnering with industry in large non-industrialized countries that have a sophisticated vaccine industry (e.g. Brazil, China, India and Indonesia).

Whereas both approaches could be useful and should be pursued, many considered that the former would be ideal if it could be achieved. Much discussion therefore focused on what would be required to entice major vaccine manufacturers to become intimately involved in accelerated joint development projects for developing-market vaccines. From the animated and highly productive discussions that ensued on

this theme, to which both public sector and industry representatives actively contributed, the following points were noted:

- Each vaccine selected should have intellectual property coverage which the partnering company would license;
- If the vaccine has a potential market among travellers in industrialized countries it would be more attractive to industry;
- The public sector would have to convincingly quantify the extent to which the vaccine would be used in developing countries so that the requirements for production facilities can be matched with the projected markets in those countries;
- The costs of preparing early pilot-lot formulations may have to be either entirely borne by the public sector or shared on a disproportionate basis, with the public sector paying the majority;
- Expenses for carrying out the early Phase I and II clinical trials, when the risk of failure is highest (that is, when odds are highest that the vaccine may prove to be unacceptably reactogenic or inadequately immunogenic), would have to be borne by the public sector;
- The public sector would have to contribute substantially to the costs and to performance of the pivotal pre-licensure Phase III efficacy trial, including site preparation.

If the public sector assumes the high risk portions of the development costs of a vaccine, once it is licensed by regulatory authorities and manufactured in large scale, the unit price of the vaccine in developing countries (as opposed to the price for travellers) should reflect the limited investment in R&D for that vaccine by the company (many of the costs will have been borne by the public sector partners).

4.1.2 Not-for-profit companies and virtual corporations

One attractive approach to create symbiotic public–private partnerships to develop developing-market vaccines is to establish a not-for-profit (NFP) company, funded by the public sector. The NFP company would be dedicated to foster development of the specific vaccine to the point of licensure and assure manufacture of sufficient vaccine for use in developing countries. Since such a company would focus on development of a single product, there would be no competing internal projects of higher priority. The NFP company would also have the freedom to design the product specifically for use in a developing-country setting, rather than adapt a product originally designed for an industrialized country.

Such a partnership can take several forms. The fastest and most efficient approach would be to form an alliance between the NFP company and an industrial vaccine manufacturer. Vaccine development could proceed on a fast track. Once pilot formulations are available, studies could rapidly move into target populations in developing countries. When more definitive formulations become available after scale-up, the fill, release, quality control and clinical, regulatory and licensure activities for the vaccine could be the responsibility of the NFP company; these activities would not compete for internal resources of the commercial company.

The International AIDS Vaccine Initiative (IAVI) serves as a model of a virtual corporation. While IAVI is a not-for-profit entity committed to AIDS vaccine development, it is managed in a private sector style and operates in a business-like manner. For each specific task in the AIDS vaccine development process, IAVI seeks a suitable academic group or company with a track record of expertise in that area and contracts their services.

4.1.3 Pilot-lot formulations as a model: alternative "innovative" strategies for accessing pilot-lot capacity

In order to devise ways to increase the access to pilot-lot formulations for research teams working on developing-market vaccines of interest to GAVI, three models were discussed.

A GAVI/industry collaborative facility: This could be either a "virtual" or a real institute, or both, depending on the specific vaccine development projects. Such a GAVI/industry facility would be limited to producing pilot lots of developing-market vaccines of little interest to industry. However, because of the complexity of product development, this facility should be managed by individuals with industry experience. One possibility would be that every major vaccine company would sponsor a development project, putting a senior development person at the disposal of the institute as an expert to follow up a particular project. One could envisage professionals hired by the institute or put by the companies at the disposal of the institute as a kind of "sabbatical". Operational costs would have to be contributed by GAVI's partners. Close collaboration with scientists of the original discovery group would be required for success.

A non-profit, self-supporting GAVI facility: A second scenario involves the acquisition of a facility using private funds and managed by a private contractor. The facility would be self-supporting but non-profit. A scientific advisory board would guide the vaccine development decisions and an advisory committee composed of industrial scientists would provide practical guidance and perhaps steer future interest in products developed under this concept.

Public/private collaborations: The third model is based on private–public partnerships between academia and industry. Academia would receive funding for the development of vaccine candidates in partnership with industry. Intellectual property rights developed during the partnership would revert to the funding body if milestones were not met. A royalty arrangement would also be developed which would benefit the funding agency.

There was agreement that solving the problem of access to pilot-lot formulations is one of the most important generic obstacles that GAVI should address in its research and development agenda. There was also a consensus recommending that a GAVI Task Force on Research and Development should explore the various options in greater depth.

4.2 GAVI "pull" strategies for research and development

The Pre-Task Force on Research and Development focused on ways to "push" the research and development agenda for the development of developing-market vaccines. In order to provide a broad picture of the different ways in which GAVI will be attacking the overall problem, several members of the GAVI Task Force on Financing reviewed the ways in which that Task Force is attempting to create "pulls", i.e. incentives for industry to invest in research and development for developing-market vaccines.

One of the impetuses for the creation of the GAVI Task Force on Financing was to identify and address the issues of critical importance to industry that influence whether or not they will become involved in the effort to develop vaccines against diseases of primary interest for developing country use. One of the central issues was that of credibility. Specifically, industry related its need to be able to demonstrate that there is a credible market for the new products that it develops. The failure of countries in the developing world to include yellow fever vaccine and hepatitis B vaccines in their national immunization programmes, despite WHO recommendations and the low cost and high cost-benefit ratio for these vaccines, indicates that considerable education and advocacy remains to be done. Five key items were identified that are essential in creating the industrial incentive for future investment. These include:

- Stimulating national demand;
- Developing guarantee purchase mechanisms;
- Providing realistic forecast of vaccine use;
- Protecting intellectual property rights; and
- Increasing government ownership/responsibility for national immunization systems, including the introduction of new vaccines.

Affirming this viewpoint, the industry representatives at the meeting emphasized that it is the likelihood of a satisfactory return on investment that is the most fundamental concern for industry. Five items were identified as factors that could "pull" industry into this arena. They were summarized as real corporate motivation and include:

- Availability of infrastructure for vaccine distribution;
- Advocacy for the vaccine, specifically consensus about the desirability of a product;
- Demonstration that developing countries are credible and sustainable markets for new products;
- Vaccine prices in these that provide a reasonable margin of profit.

It was the general view of the Pre-Task Force participants that programmatic implementation of Hib and HBV more widely in developing countries will be crucial for establishing credibility for the involvement of industry in participating in research and development for vaccines against parasitic diseases, diarrhoeal diseases, and other priority diseases.

4.3 What role does intellectual property play in research and development for developing-market vaccines?

Protection of intellectual property through patents is an important incentive to industry, as it assures that their investment will be protected for a number of years, once a vaccine reaches licensure and can be commercialized. Thus, strong intellectual property positions stimulate the vaccine development process and can hasten its pace. Equally important to intellectual property, is the credibility of the licensee. However, the most critical issue of all appears to be the marketability of the product.

Difficulty in paying patent costs, especially in purely academic situations, was identified as a barrier. Recognizing that protection of intellectual property through the successful issuance of patents is a key to eventually being able to attract industrial partners, the high costs of filing and maintaining patents for academic investigators in industrialized as well as developing countries was pointed out. This is a fundamental problem that must be solved. If not, many of the basic research discoveries made in academic institutions that can form the basis of constructing vaccine candidates against diseases of importance to the developing world will not be protected and, therefore, will not be of interest to future industrial partners. Two possible options were proposed. The first, is to try to partner early with industry so that the industrial partner will absorb these costs. In fact, in the current reality, this is unlikely to succeed for the various reasons already cited that explain why major industry has little interest in developing-market vaccines. At present there is no rationale for industry to pay the patent filing costs for vaccines in which they have little interest in investing. The second option is more realistic and could constitute an important contribution by GAVI. When no industrial sponsor comes forth, a request could be made for GAVI to pay the patenting costs, perhaps through the research and development window of GAVI's Global Fund for Children's Vaccines; in exchange, royalties from the ultimate sales of the vaccine could go back into the Fund. In this way, several hurdles would be overcome: (a) intellectual property would be protected by acquisition of patents so that at a later point, if the discovery matures into a vaccine candidate, it may be possible to attract an industrial partner; (b) this may help a vaccine against a disease of primary interest to developing countries to be developed to the point of licensure; (c) assuming that other segments of GAVI successfully create guaranteed markets for the use of this vaccine, a proportion of the royalties from sales of the vaccine would be returned to the GAVI Fund to be used for other patent filings. Obviously, many specifics of such an approach would have to be worked out and this would have to be limited to the specific vaccines that are highest on GAVI's priority list, presumably to be prepared by a future GAVI Task Force on Research and Development.

Another instance in which intellectual property impacts on vaccine development is when there are different owners of distinct intellectual properties, all of which may be required to create the most scientifically rational vaccine. This is a complex issue. Ideally, in view of the global public health imperative for the vaccine, GAVI could somehow foster an accommodation among the parties that would allow rational vaccine development research to proceed.

4.4 Coordination of global efforts

The participants concluded that a GAVI Task Force on Research and Development should respect the energy, ingenuity and innovation of the various existing independent projects, programmes and research groups globally that are working to develop vaccines to prevent the diseases of developing countries. On the other hand, because resources are limited and the global needs are many, participants argued that a Task Force that can enhance communication among disparate groups in the research community, convey global priorities, establish liaisons and collaborations (between North and South, bench and clinical, public sector and private industry), solve certain generic problems (e.g. access to pilot lots, simplification of clinical trials) and provide global leadership, would be an important step forward.

5. Summary points, strengths, gaps and items for action

- GAVI should foster research and development of developing-market vaccines against diseases for which the burden is largely limited to the developing countries.
- A Task Force on Research and Development should be established to join the other three Task Forces that assist the GAVI Secretariat and Working Group in achieving GAVI's objectives.
- The GAVI Task Force on Research and Development should work with WHO, epidemiologists from developing countries, industry, UNICEF, World Bank and other partners to set the priorities for which developing-market vaccines, in addition to those for HIV, malaria and tuberculosis, are most needed.
- Where epidemiologic, microbiologic or parasitologic data are deemed to be insufficient to allow a fair assessment of disease burden, the collection of those data should be undertaken.
- A GAVI Task Force on Research and Development should "push" the development of these vaccines by:
  - fostering partnerships with industry;
  - assisting in obtaining patent protection;
  - facilitating access to pilot-lot formulations (through various mechanisms);
  - facilitating sponsorship (i.e. financial support) for clinical trials;
  - exploring ways to make clinical trials simpler and more economical;
- The global capacity for production of pilot-lot formulations of different types of vaccine under GLP and GMP should be catalogued (and periodically updated).
- The GAVI Task Force on Research and Development should, in collaboration with DMID, NIAID, review future annual issues of the Jordan Report prior to publication to ensure that progress on research on the GAVI priority vaccines is contained therein.
- The GAVI Task Force on Research and Development should oversee the preparation of a catalogue of clinical trials facilities in industrialized and developing countries with experience or potential for evaluating developing-market vaccines in Phase I–IV clinical trials. (This must be annually updated.)
- GAVI should foster the viability of the clinical trial research units in Africa,

Asia and Latin America, that have established track records in performing GCP clinical trials in adult and paediatric populations.

- Non-profit companies and "virtual corporation" models are attractive strategies to be pursued for nurturing the development of certain developing-market vaccines.
- More direct forms of academia/industry partnership should also be encouraged.
- The GAVI Task Force on Research and Development should actively explore opportunities in large developing countries such as Brazil, China, India and Indonesia that have large-scale manufacturing capacity and strong research capability.
- The "push" activities of the GAVI Task Force on Research and Development should be coordinated with the "pull" efforts of the GAVI Task Force on Financing to achieve synergy.

Table 1. Priority ranking of developing-market diseases

Results of a highly informal, preliminary survey among meeting participants to ascertain the priority ranking of developing market diseases that should be targeted for accelerated research and development.

New vaccines (none currently licensed)	Overall ranking
Shigella	1 (73)
Dengue	2 (66)
ETEC	5 (49)
Schistosomiasis	7 (24)
Leishmania	8 (21)
Hepatitis C/E	9 (17)
Improved vaccines (licensed vaccines exist)	
Typhoid	3 (56)
Group A meningococcus	3 (56)
Japanese encephalitis	6 (42)

(counting: first rank = 4 points, second rank = 3 points etc) This is a ranking of 29 responses. Respondents identified their areas of expertise as including basic vaccine development, clinical vaccinology, immunology, industrial vaccine development, microbiology, public health, epidemiology, parasitology, regulatory affairs and jurisprudence.

Table 2. Sensitivity analysis for the burden of *Shigella* disease in developing countries

Age strata	**0–11 months**		**1–4 yrs**		**5–14 yrs**		**15–59 yrs**		**>60 yrs**	
Total population	125 000 000		450 000 000		1 011 000 000		2 647 000 000		330 000 000	
Disease burden	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**
Total diarrhoea episodes (TD)										
No. episodes person/yr	2.7	5.0	1.7	3.0	0.65	0.65	0.5	0.5	0.69	0.69
Total (TD) episodes/yr	337 500 000	625 000 000	765 000 000	1 350 000 000	657 140 250	657 140 000	1 323 304 000	1 323 304 000	227 320 500	227 320 500
Diarrhoea episodes in domicile (DD)										
No. episodes (% of TD)	297 675 000 (88)	551 250 000 (88)	703 035 000 (92)	1 240 650 000 (92)	643 997 450 (98)	643 997 450 (98)	1 296 837 920 98)	1 296 837 920 (98)	222 774 090 (98)	222 774 090 (98)
No. *Shigella* (% of DD)	5 954 000 (2)	27 563 000 (5)	42 182 100 (6)	235 723 500 (19)	6 439 970 (1)	19 319 920 (3)	12 968 380 (1)	38 905 140 (3)	2 227 740 (1)	6 683 220 (3)
Diarrhoea episodes in outpatients (OD)										
No. episodes (% of TD)	34 763 000 (10)	64 375 000 (10)	60 435 000 (8)	106 650 000 (8)	13 142 810 (2)	13 142 810 (2)	26 466 080 (2)	26 466 080 (2)	4 546 410 (2)	4 546 410 (2)
No. *Shigella* (% of OD)	695 000 (2)	19 313 000 (30)	7 856 550 (13)	41 593 500 (39)	657 140 (5)	2 759 990 (21)	793 980 (3)	7 145 840 (27)	409 177 (9)	1 545 780 (34)
Diarrhoea episodes hospitalized (HD)										
No. of episodes (% of TD)	5 063 000 (2)	9 375 000 (2)	1 530 000 (0.2)	2 700 000 (0.2)						
No. with *Shigella* (% of HD)	203 000 (4)	1 031 000 (11)	122 400 (8)	864 000 (32)						
No. *Shigella* episodes										
Subtotal, by age strata	6 852 000	47 907 000	50 161 050	278 181 000	7 097 115	22 079 910	13 762 360	46 050 980	2 636 920	9 774 780
Subtotal, by age group	**Low:** 57 012 300		**High:** 326 087 250			**Low:** 23 496 390		**High:** 89 488 332		
Total annual *Shigella* episodes				**Low: 80 508 690**		**High: 415 575 580**				
Mortality	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**
Mortality from HD with *Shigella*										
Uncorrected (% of HD)	28 150 (14)	143 340 (14)	11 510 (9)	81 220 (9)	53 890 (8)	226 320 (8)	65 110 (8)	585 960 (8)	33 553 (8)	126 750 (8)
Corrected for out-of-hospital mortality	112 600 (4x)	1 433 440 (10x)	46 020 (4x)	812 160 (10x)	215 540 (4x)	2 263 190 (10x)	260 430 (4x)	5 859 590 (10x)	134 210 (4x)	1 267 540 (10x)
Subtotal, by age group	**Low:** 158 610		**High:** 2 245 600			**Low:** 610 180		**High:** 9 390 320		
Total annual *Shigella* deaths			**Low: 768 790**		**High: 11 635 920**					

Source: Kotloff et al, *Bull WHO*, 1999, 77:651–666

Table 3. Partial survey of the public sector clinical trial facilities in industrialized countries that have evaluated developing-market vaccines

A partial survey of the public sector clinical trials facilities in industrialized settings that have a track record in evaluating developing-market vaccines such as vaccines against malaria, cholera, typhoid fever, *Shigella* dysentery and enterotoxic *Escherichia coli* (ETEC) diarrhoea and dengue fever

Institution	Location	Phase I	Phase II	Phase IIB (challenge)	Phase III[b]	Phase IV
WRAIR/NMRI[a]	Silver Spring, Maryland	Malaria *Shigella* ETEC Cholera Dengue	Malaria *Shigella* ETEC Cholera Dengue	Malaria *Shigella* ETEC Cholera	Malaria ETEC Cholera Typhoid	
Center for Vaccine Development, U. of Maryland (NIH VTEU network[c])	Baltimore, MD	Malaria *Shigella* ETEC Cholera Typhoid Dengue	Malaria *Shigella* ETEC Cholera Typhoid Dengue	Malaria *Shigella* ETEC Cholera	Typhoid *Shigella* Cholera	Hib conjugate
U. of Cincinnati (NIH VTEU network)	Cincinnati, Ohio	Cholera	Cholera	Cholera		
Dept. of Microbiology, Baylor Univ.	Houston, Texas	Malaria	Typhoid			
Dept. of Med. Microbiology, Uni. of Gothenburg	Gothenburg, Sweden	Cholera ETEC	Cholera ETEC		Cholera ETEC	
Karolinska Institute	Stockholm, Sweden	*Shigella* Typhoid	*Shigella* Typhoid	*Shigella* Typhoid		
Queensland Institute of Medical Research	Brisbane, Australia	Malaria	Malaria			
Israel Defense Force	Israel	*Shigella* ETEC	*Shigella* ETEC		*Shigella* ETEC	
St. George's Hospital Medical School	London, UK	Cholera Typhoid	Cholera			

[a] WRAIR = Walter Reed Army Institute of Research; NAMRI = Naval Medical Research Institute

[b] With the exception of Phase III studies carried out by the Israel Defense Forces, the other Phase III and Phase IV trials performed by the institutions listed in this table were in carried out in collaboration with institutions in developing countries listed in Table 4.

[c] There are several other independent units in the NIH VTEU (Vaccine and Treatment Evaluation Units) network. However, they do not have an established track record of working on developing-market vaccines.

Table 4. Partial survey of the public sector clinical and field trial sites in developing countries that have a track record of evaluating developing-market vaccines.

Institution	Location	Phase I	Phase II	Phase III	Phase IV
Medical Research Council Laboratories	Fajara, the Gambia	Malaria HBV Hib conjugate Pneumo conj. Mening. Conj.	Malaria HBV Hib conjugate Pneumo conj. Mening. conj.	Malaria HBV Hib conjugate Pneumo conj.	
National Institute for Health R&D & NAMRU-3	Jakarta, Indonesia		Cholera Typhoid	Cholera Typhoid	
AFRIMS	Bangkok, Thailand		Japanese B encephalitis Hepatitis A	Japanese B encephalitis Hepatitis A	
NAMRU-2	Cairo, Egypt	ETEC Typhoid	ETEC Typhoid	ETEC Typhoid	
CVD-Chile	Santiago, Chile	Cholera Typhoid Hib conj. Pneumo conj.	Cholera Typhoid Hib/pneumo conj. Mening. conj.	Typhoid Pneumo conj.	Hib conjugate
Institute of Nutrition NMRI Detachment	Lima, Peru Lima, Peru		Cholera Cholera	Cholera Cholera	
Instituto Nacional de Salud Publica	Cuernavaca, Mexico		Cholera		
Inst. de Medicina Tropical	Caracas, Venezuela		Malaria	Malaria	
ICDDR,B	Bangladesh	Cholera ETEC *Shigella*	Cholera ETEC *Shigella*	Cholera	
Vaccine Trial Centre, Mahidol University	Bangkok, Thailand	Cholera Dengue	Cholera		
Ifakara Centre & Unidad de Epidemiologia, Hospital Clinic, Barcelona, Spain.	Ifakara, Tanzania.	Malaria	Malaria	Malaria	
Lanzhou Institute of Biological Products	Lanzhou, China	*Shigella* Typhoid Cholera	*Shigella* Typhoid Cholera	*Shigella* Typhoid	
Nat. Inst. Hygiene & Epid.	Hanoi, Viet Nam	Cholera Typhoid	Cholera Typhoid	Cholera Typhoid	

NAMRU = U.S. Naval Medical Research Unit; NMRI = U.S. Naval Medical Research Institute; AFRIMS = Armed Forces Medical Research Institute; CVD-Chile = Centro para Vacunas en Desarrollo, Chile; ICDDR,B = International Center for Diarrheal Diseases Research, Bangladesh.

Table 5. Partial survey of the public sector clinical and field trial sites in developing countries that are being prepared to evaluate developing-market vaccines but that have not yet undertaken clinical trials with these vaccines

Institution	Location	Phase I	Phase II	Phase III	Phase IV
Papua New Guinea Institute of Medical Research	Madang, Papua New Guinea	Planned	Planned	Planned	
International Vaccine Institute	Seoul, Korea	Planned	Planned	Planned	
Noguchi Memorial Inst. for Medical Research & Navrongo Health Research Centre & NMRI	Navrongo, Ghana	Planned	Planned	Planned	
Centro de Investigaci ó n en Salud de Manhiça & the Unidad de Epidemiología, Hospital Clinic, Barcelona	Manhiça, Mozambique	Planned	Planned	Planned	
CVD, U. of Maryland & U. of Mali Malaria Research & Training Center	Bandiagara, Mopti Region, Mali	Planned	Planned	Planned	

NMRI = U.S. Naval Medical Research Institute; CVD = Center for Vaccine Development

Annex 1: Agenda

Thursday, 4 November 1999

Day 1 — Co chairs: Professor Mike Levine and Dr Jeffrey Almond
Rapporteur: Dr Carole Heilman

Welcome and introductions

08:30-08:40	An overview of GAVI:	Dr Tore Godal
08:40-08:45	WHO V&B/VAD	Dr Teresa Aguado
08:45-08:50	WHO CRD/TDR	Dr Farrokh Modabber
08:50-09:05	Rationale and expected outcomes of the meeting (in particular, mapping the gaps in the R & D infrastructure)	Prof Mike Levine

Vaccines for which research and development activities are languishing

09:05-09:10	Defining terms	Prof Mike Levine

Is there an unacceptable gap in epidemiologic information?

09:10-09:25	Do we have sufficient disease burden data and economic impact data to prioritize the target diseases? If not, where are the gaps?	Dr John Clemens
09:25-09:40	The 1999 Institute of Medicine report, a strategy for setting vaccine development priorities. Can it and should it be applied to developing country diseases?	Dr Regina Rabinovich
09:40-09:55	Discussion	
09:55-10:00	Conclusions and recommendations	

For the target vaccines, is there a gap in our ability to identify track and update, in a timely fashion, the status of vaccine development activities, worldwide?

10:00-10:05	A data base to track the public and private research development efforts worldwide that focus on the target vaccines and the immunization strategies	Prof Mike Levine

Thursday, 4 November 1999 (*continued*)

10:05-10:10	The "State of the World's Vaccines and Immunization"	Dr Bjorn Melgaard
10:10-10:15	The annual Jordan Report	Dr Carole Heilman
10:15-10:25	Discussion	
10:25-10:30	Conclusions and recommendations	Prof Douglas Young
10:30-10:45	*Coffee break*	

Identifying generic gaps in the global research and development capability

10:45-11:00	Gaps in pilot lot formulations	Dr Kathryn Zoon
	1.1 A regulator's perspective of pilot lot formulations	
	1.2 What is the global capacity for pilot lot formulations for the target vaccines?	
	1.2.1 What public research institutions, academia and small vaccine biotech companies do:	
11:00-11:05	NIH, USA	Dr Carole Heilman
11:05-11:10	Dep't of Defense, USA	Dr Stephen Hoffman
11:10-11:15	KTL	Prof Helena Mäkela
11:15-11:20	RIVM, the Netherlands	Dr Jan Hendriks
11:20-11:25	Future IVI capability	Dr John Clemens
11:25-11:30	Peptide Therapeutics/Oravax	Dr Michael Darsley
11:30-11:45	Discussion	
11:45-11:50	Summary and conclusions	Dr Carter Diggs
	1.2.2 How industrial vaccine manufacturers provide pilot lot formulations for lower priority projects:	
11:50-11:55	SKB	Dr Francis André
11:55-12:00	Wyeth-Lederle	Dr Kerim Chitour
12:00-12:05	Pasteur Mérieux Connaught	Prof Jeffrey Almond
12:05-12:10	Chiron	Dr Giuseppe Del Giudice
12:10-12:25	Discussion	
12:25-12:30	Summary and conclusions	Dr Alan Shaw
	1.2.3 What is the capacity for GMP pilot lot production by private and public vaccine manufacturers in developing countries?	
12:30-12:35	Hong Kong Institute of Biotechnology Ltd	Dr Philip Ngai
12:35-12:45	Discussion	
12:45-12:50	Summary and conclusions	Prof Duc Trach
12:50-14:00	*Lunch*	

1.2.4 How can we improve access to pilot lot formulations, including strategies for funding?

14:00-14:10	Public/private partnerships to provide "first class" pilot lot formulations	Prof Mike Levine
14:10-14:25	Innovative approaches	Mr Jacques Martin
14:25-14:40		Dr Stanley Plotkin
14:40-14:50	Can philanthropy finance production of pilot lots of selected vaccines?	Dr Regina Rabinovich
14:50-15:05	Discussion	
15:05-15:10	Summary and conclusions	Prof Jeffrey Almond

2. Gaps in clinical trials

2.1 Are there ways to simplify and economize the performance of GCP clinical trials for the target vaccines?

15:10-15:25	Perspective of a clinical vaccinologist	Dr Rosanna Lagos
15:25-15:40	Perspective of regulatory agencies	Dr Kathryn Zoon
15:40-15:55	Discussion	
15:55-16:00	Summary and conclusions	Dr Francis André
16:00-16:15	*Coffee break*	

2.2 What is the global infrastructure for performing clinical trials of the target vaccines?

Commentaries from illustrative sites and facilities:

16:15-16:20	NIH VTEUs, USA	Dr Carol Heilman
16:20-16:25	Dep't of Defense, USA	Dr Stephen Hoffman
16:25-16:30	Europe	Dr Joachim Hombach
16:30-16:35	Vaccine Trial Centre, Mahidol University	Prof Natth Bhamarapravati
16:35-16:40	IVI	Dr John Clemens
16:40-16:55	Discussion	
16:55-17:00	Summary and conclusions	Prof Ramesh Kumar

3. Gap in new generic technologies

3.1 Characteristics of future vaccines that can simplify and economize immunization and increase compliance:

Ability:

3.1.1 to be given in combination with other vaccines;
3.1.2 to be administered by non-parenteral (mucosal or transcutaneous) routes;
3.1.3 to immunize with only one or two doses;
3.1.4 to immunize very young infants (< 3 months of age);
3.1.5 to be thermostable.

Thursday, 4 November 1999 (*continued*)

17:00-17:10	Dr Teresa Aguado	
17:10-17:15	Dr John Lloyd	
17:15-17:30	Discussion	
17:30-17:35	Summary and conclusions	Jean-Francois Martin

Friday, 5 November 1999

Day 2	Co chairs: Professor Mike Levine and Dr Francis André Rapporteur: Dr Carole Heilman	
08:30-08.45	The GAVI "pull". Efforts to create incentives for investments	Dr Steve Landry
08:45-09:00	in R & D for target vaccines by creating guaranteed markets and other mechanisms	Dr Francis André
09:00-09:15	Discussion	
09.15-09:35	Intellectual property issues and rational vaccine development	Ms Elizabeth Fuller
09.35-09:40	Comments on intellectual property issues	Dr Roy Widdus
09:40-10:00	Discussion led by Dr Luis Barreto	
10:00-10:15	*Coffee break*	

What mechanisms can provide a global overview and coordination of research and development efforts on the target vaccines and immunization strategies?

10:15-10:25	How do investigators in developing countries communicate their views on what should be the global research prioities?	Dr Steven Obaro
10:25-10:50	Discussion	
	Summary and conclusions	Prof Helena Mäkela

Final recommendations and overall summary of the meeting

10:50-11:20	Finalization of recommendations	
11:20-11:50	Overall summary of meeting and commentary	Sir Gustav Nossal
11:50-12:00	Final comments for GAVI	Prof Mike Levine and Dr Tore Godal
12:00	*Adjourn*	

Annex 2:
List of participants

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