Sida Evaluation 07/09

The Relevance and Future Role of the International Vaccine Institute (IVI)

2000–2006

Leif Gothefors
Marita Troye-Blomberg
Lars Åke Persson

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Authors: Leif Gothefors, Marita Troye-Blomberg, Lars Åke Persson.

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SWEDISH INTERNATIONAL DEVELOPMENT COOPERATION AGENCY
Address: SE-105 25 Stockholm, Sweden. Office: Valhallavägen 199, Stockholm
Telephone: +46 (0)8-698 50 00. Telefax: +46 (0)8-20 88 64
E-mail: sida@sida.se. Homepage: http://www.sida.se

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Executive Summary

The International Vaccine Institute (IVI) has a mission to contribute to the reduction of vaccine preventable diseases in developing countries by research that generates the evidence needed for rational introduction of new vaccines, supported by programs of basic and applied laboratory research, product development, training and technical assistance. IVI was established a decade ago as part of a larger public sector process of change where several organizations are acting in mobilizing resources for procurement and distribution of vaccines in developing countries.

This evaluation was commissioned by Sida. The purpose was to evaluate progress of IVI in relation to its stated mission and to focus the future direction and provide recommendations that could be relevant for IVI and its stakeholders as well as for Sida.

The role of IVI is unique and an excellent complement to other activities in this area. It fills in many gaps in the public sector's efforts to develop and deploy new vaccines for the poor in developing countries by virtue of: 1) its broad range of in-house technical activities, which encompass both research and applied vaccine development, and which span the entire vaccine continuum from vaccine discovery, through clinical trials, and downstream economic, policy, and socio-behavioural analyses; 2) its focus on many different vaccines and diseases, which enhances the credibility of the IVI as an "honest broker" that is not wedded to a particular vaccine or disease; 3) its focus on cross-cutting issues such as vaccine safety, including the assessment of uncommon but serious potential vaccine side-effects, which have tended to be neglected on the world stage because of the disease-driven focus of most global initiatives; 4) its international legal status and its flexibility to work with the private sector, which have allowed the IVI to establish integrated collaborating networks of other international organisations; institutions in developing countries; universities and government scientific institutions, and other technical organisations in the industrialized world; and industry in both industrialized and developing countries, which have allowed the IVI to create unique programs of vaccine development and accelerated introduction, such as the Diseases of the Most Impoverished (DOMI) Program, a program to accelerate the development and introduction of new vaccines against cholera, shigellosis and typhoid fever; 5) its demonstrated ability to transfer vaccine production technologies to vaccine producers in developing countries, which are becoming increasingly important to the supply of vaccines to developing countries; and 6) its wide-ranging programs of capacity building of vaccine professionals in developing countries, in areas as diverse as vaccine clinical evaluation, social science research, and vaccine production and regulation, which are critical to empowering developing countries to produce and to rationally introduce new vaccines in a sustainable fashion.

IVI has shown impressive growth and is well on track in relation to its stated mission and aims. The contributions in translational research and training are especially impressive, and it has today exerted major impact on policy decisions about vaccine development and introduction for a number of diseases. This is an area where further geographical expansion is recommended. So far the majority of IVI's activities have been in Asian countries. Many of the global challenges are found in Africa, where IVI's niche and special competence could be of great value in addition to the major investments done by GAVI and other international actors.

The evaluation recommends that the further expansion of IVI's activities mainly is done by including new countries and collaborating partners rather than expanding the vaccine portfolio.

The evaluation recommends that IVI's laboratories primarily should provide support to the translational research and reduce the number of smaller projects.

In order to further strengthen the translational research and the use of the knowledge that is generated we propose that IVI establishes a policy unit that could strengthen its unique contributions among present international vaccine initiative players. We also propose that IVI's programs of transfer of technologies be expanded beyond Asia to include Africa and South America. A further expansion of the unique monitoring work of vaccine safety is another recommended priority area.

A large number of countries and international agencies make large investments in vaccines these days. To a large extent those activities include procurement and distribution of vaccines to low-income countries. IVI and its supporters should improve the communication of IVI's unique role and contribution to a sustained bridging of the gap in child health between high- and low-income countries.

IVI has shown an impressive increase in funding over these years. However, it is very much dependent on one major donor. IVI, its board, its signatories and other interested parties should make a concerted effort to increase the financial support, to expand the number of signatories and donors, and to increase the proportion of core support in order to achieve financial sustainability.

Based on our findings and analysis of IVI's role and performance we propose that Sida continues and considerably increases its core support to IVI when entering into the next agreement period.

Introduction

The International Vaccine Institute (IVI) was established on the campus of Seoul National University in the Republic of Korea in October 1997 as an autonomous international organisation under the Vienna convention of 1969. This was the result of a process initiated by United Nations Development Programme (UNDP) already in 1992, to meet a need for an international non-profit organisation that could assist efforts to close the gap between vaccines for the developing world versus the industrialised world by conducting research and delivering technical assistance. The birth and growth of IVI is part of a larger public sector process of change with several major actors, e.g. the Global Alliance for Vaccines and Immunizations (GAVI), which has been very successful in mobilising resources for procurement and distribution of vaccines for developing countries and later also for the investment in new vaccines. IVI's signatories currently include 39 countries and the WHO. Sweden is one of the signatory countries and has been so since the inception of IVI.

Sida/SAREC has supported IVI since 2002 and has since then contributed with 12 MSEK. The ongoing agreement covers 2005–2007. The reason why Sida is commissioning an external evaluation is partly because this was requested by Sida's Research Committee in February 2005 as a precondition for continued and perhaps increased support. Secondly, it is Sida's policy to regularly evaluate the organisations receiving support from Sida. Thirdly, given that there are so many new actors in the field of vaccine research, it is considered by Sida to be very timely to evaluate IVI.

The purpose of this evaluation is to "assess the relevance, efficiency, effectiveness and impact of IVI in relation to its stated mission and functional structures and operating environment from 2000 until now and also into the future". The scope of the evaluation is to focus on future direction and management of the programs resulting in concrete and realistic recommendations, especially regarding program activities and interaction/collaboration with other key stakeholders in the area of vaccine research and vaccine programs.

As requested in the terms of reference (Annex 1), the disease focus of the evaluation is on *diarrhoeal diseases,* i.e. the Diseases of the Most Impoverished (DOMI) Program of the IVI, which focuses on cholera, shigellosis and typhoid) as well as rotavirus diarrhea, and on diseases caused by *respiratory tract pathogens,* i.e. bacterial meningitis and pneumonia. In addition, Japanese encephalitis and dengue will be included. The programs or dimensions to be included in the evaluation were set to be:

- *Translational research,* e.g. burden of disease studies, clinical studies of experimental vaccines, cost-effectiveness studies and policy studies
- *Vaccine safety*
- *Laboratory research* that started in 2004
- *Vaccine development and process research*, e.g. the development of a *Shigella* ribosomal vaccine prototype
- *Technical assistance and training*, e.g. training in vaccine production and regulation, training in good clinical practice (GCP), training in vaccinology and advanced laboratory techniques

The methodology used for the evaluation includes review of previous reports, results of evaluations and memoranda from IVI and Sida, visits to IVI and to collaborating partner institutions in Kolkata and Hanoi for presentations of ongoing work, discussions and interviews with relevant key personnel. Further, contacts were taken with several other partners and key stakeholders within the vaccine area. The SWOT analysis conclusions and recommendations were developed together by the review team and approved by all members. The views expressed are those of the review team and do not necessarily

reflect those of the contact persons interviewed. The report is provided for the benefit of IVI and is primarily aimed for the Board and Donors as a support material in their work to sustain and further develop IVI.

The International Vaccine Institute (IVI)

The Goal is that IVI *is founded on the belief that the health of children in developing countries can be dramatically improved by the development, introduction, and use of new and improved vaccines and that these vaccines should be developed through a dynamic interaction among science, public health, and industry.*

IVI's Mission is to *contribute to the reduction of vaccine preventable diseases in developing countries by collaborative research that generates the evidence needed for rational introduction of new vaccines, supported by programs of basic and applied laboratory research, product development, training, and technical assistance.*

Over the past 10 years since its inception IVI has established major research programs mainly in Asia, but also to some extent in Africa and Latin America providing evidence to inform policy for rational introduction of vaccines. These programs of research have addressed new vaccines against cholera, shigellosis, typhoid fever, rotavirus, *Haemophilus influenzae* B, pneumococcus meningococcus, dengue fever and Japanese encephalitis. The IVI has also developed model systems for assessing safety of vaccines. From 2004 a program of laboratory research has been initiated that addresses topics in immunology, molecular biology, and vaccine development. Further, an impressive training program has been running, technical assistance has been provided, and a substantial network has been developed of partner institutions, collaborating laboratories and vaccine producing companies.

IVI has given priority to vaccines against diseases of special importance in low- and middle-income countries. These selected diseases and pathogens are cholera, shigellosis and typhoid fever (DOMI) but also Japanese encephalitis and infections caused by *Haemophilus influenzae* type b, *Streptococcus pneumoniae, Neisseria meningitidis,* rotavirus, dengue virus and enterotoxigenic *Escherichia coli.*

Activities of the IVI focus on filling major gaps that exist in translational research, laboratory research, product development, technical support and capacity building for vaccines of priority concern to developing countries. IVI's in-house expertise provides a strong basis to assist in training programs, to strengthen scientific research in relevant areas, to augment production quality control and regulatory skills in developing country institutions to accelerate the introduction of vaccines.

Since the inception of the institute it has been evaluated once in its early stages of implementation (2000); an evaluation that was commissioned by UNDP. Many of the recommendations were linked to IVI's relationship with UNDP, e.g. it recommended a continued UNDP commitment, both morally and financially. However, because of changing priorities at the UNDP, it no longer provides core support to IVI. Other recommendations were that cooperation and communication between IVI and GAVI should be continued and expanded in well-defined areas, that IVI should strive to develop itself into a fully international institution and that future research efforts of the IVI should be closely linked to its ongoing activities in epidemiological field studies of disease burden and vaccine effectiveness. Further, IVI was recommended to communicate more effectively its existence, mandate and mission to developing countries, to private industry and donors. Finally, in recognition of its status as an independent international institute, the evaluation performed by UNDP suggested that IVI should ensure continued external review of its future activities to ensure objectivity and transparency.

Findings

Translational research

One of the major tasks of IVI is to promote implementation of new knowledge in the vaccine area; from bench to practical application in communities and countries. This is done by translating knowledge and evidence derived from a group of disciplines into policy decisions that result in rational use of vaccines against diseases of great public health importance in immunization programs of the developing world. Great emphasis is given to the production also within the region where such vaccines are to be used especially for orphan vaccines that address important public health needs but are of limited interest to multinational vaccine producers. In its aim to narrow the gap between the rich and the poor IVI has focused on existing, new-generation vaccines that are not being used and on experimental vaccines that are in need of clinical testing in humans. Further, IVI also provides evidence to address policy uncertainties about the introduction of such vaccines.

The types of studies that are conducted by IVI include:

1. Country specific evidence of disease burden, if possible from several sites within the country. *Is there a need for this vaccine? Are there high-risk areas or populations? Do species and serotypes differ between countries or within the country?*
2. Cost of illness and vaccination? Cost-effectiveness? Cost savings from vaccination? *These new generation vaccines are often more expensive than EPI vaccines and have moderate levels and duration of protection. Careful assessment of cost and effectiveness or benefit is needed for policy development and decision making.*
3. Safety and effectiveness in the local population. *There may be differences between populations in relation to prevalence of disease, immune response and other factors.*
4. Acceptability in the community. *Local perceptions of disease, preventability and vaccination. Willingness to pay for vaccination? How much?*
5. Ability of existing health systems to successfully deliver these vaccines outside the EPI schedule. *Pilot studies to prove this would also make the vaccine known to policy makers and thus stimulate the process of decision making.*

To achieve these goals IVI is operating according to the following operating principles:

The Institute coordinates multi-country and multidisciplinary studies with standardised methods; it has a broad partnership with local and international institutions; it conducts the studies through already existing infrastructure at the country level (often Ministry of Health, and leading institutes), and it has also developed advanced training and capacity building resources.

The IVI Translational Research Program has to date exerted major impact on policy decisions about vaccine development and introduction for a number of diseases as exemplified below.

Development of an investment case to accelerate introduction of typhoid vaccines*

Type of Activity	Country						
	Bangladesh	China	India	Indonesia	Pakistan	Thailand	Vietnam
Prospective disease burden studies	X	X	X	X	X		X
Meta-analyses of disease burden	X	X	X	X	X	X	X
Assessment of feasibility, acceptability and impact		X	X	X	X		X
Cost-of-illness studies		X	X	X	X		X
Cost of delivery studies		X	X	X	X		X
Cost-effectiveness analyses		X	X	X	X		X
Assessment of demand/willingness to pay		X	X	X	X		X
Policy analysis	X	X	X	X	X	X	X

(Source: IVI, 2006)

* The X's indicate studies done in the cited countries. Countries with X's for all categories of studies were those that were predicted to be early adopters of typhoid vaccines.

During the last five years there have been a lot of activities to develop and introduce vaccines, not yet part of EPI, needed in many developing countries but not of interest to the major vaccine producers. One early project was the Diseases Of the Most Impoverished Program (DOMI) that deals with vaccines against typhoid fever, cholera and shigellosis. The activities within the Division of Translational Research has as one major cornerstone the DOMI program, supported by the Bill & Melinda Gates Foundation for 2007 with USD 2 million that also constitutes 8% of the total IVI annual budget.

The DOMI program aims to:

1. accelerate the rational introduction of existing, licensed new generation vaccines such as killed, oral whole cell-based cholera vaccine and typhoid Vi polysaccharide vaccine through generation of needed evidence through translational research studies;

2. conduct needed evaluations for vaccines which still need to undergo pre-licensure clinical trials, and

3. enable rational decision-making about use of vaccines by finding answers to the questions listed above.

What then is translational research? According to IVI it is "research that brings discovery from the bench to practical application in people" and the activities within the Institute are in a very high degree centred around this task.

Above a summary table is presented of a series of translational research studies. In order to establish accurate data, disease burden studies were initiated in several Asian countries. Using standardised epidemiological, clinical and microbiological protocols the aim was to produce information that is comparable across countries and that could be presented to those who make the decision about introduction of a new vaccine. The work at the field sites (populations 41,000–160,000) was usually conducted with local partner institutions and health ministries. To exemplify the translational research work done by IVI and its partners we have chosen typhoid as an example; see Panel 1 on page 10.

Other examples of translational research within DOMI

Cholera

During an epidemic of cholera in Mozambique, mass vaccination with rBS-WC oral vaccine produced in Sweden (two-dose, licensed for only >24 months of age) was shown to be feasible and acceptable with 90% protection against severe disease – even in this population with high HIV prevalence. Meetings with policy makers are underway.

Reanalysis of data from earlier cholera vaccine trials in Bangladesh indicates that vaccination is likely to induce herd protection, also in infants and toddlers.

Hospitalization of one patient with cholera in Indonesia would cost US$ 250. (> USD 100 paid out of pocket). Poor and middle-class people are willing to pay US$ 1 per vaccine dose. Mass immunization costs less than 1 US$/dose.

The Cholera Vaccine Initiative (Funded by the Gates foundation): The WC-only vaccine is produced and licensed only in Vietnam – never before evaluated in double-blind randomised control trials and the manufacturer is not approved by WHO. Studies have shown immune responses similar to those obtained with the rBS-WC vaccine made in Sweden. Safety and immunogenicity studies have been completed at the National Institute of Cholera and Enteric Diseases (NICED) Kolkata and a two dose, placebo-controlled, randomized efficacy trial is ongoing at NICED in Kolkata with around 70 000 participants with 61% coverage of the target population aged one year and over. The production in Vietnam (VaBiotech) has been improved with technical assistance from IVI and efforts are being made to transfer production technology to WHO-approved producers in India (Shanta Biotechnics) and Indonesia (Biofarma). The aim is to get international licensure for this vaccine. In parallel, the clinical development of the single-dose, live oral vaccine, Peru-15, which gave promising results in Phase 2 studies coordinated by the DOMI Program in Dhaka, is being undertaken of NICED in Kolkata, India and at ICDDR,B in Dhaka and Matlab, Bangladesh. This program, in which NICED, the ICDDR,B and Avant Immunotherapeutics are collaborators, will culminate with a phase 3 trial in Matlab.

Shigella

People and policymakers regard shigellosis as a significant problem where a vaccine is urgently needed. A prospective, multi-country, population-based study of *Shigella* diarrhoea in five developing (China; Indonesia; Vietnam; Pakistan; and Bangladesh) and one transitional (Thailand) countries of Asia found that shigellosis was overwhelmingly a problem of under five year-olds, with a median annual incidence rate of 17.3 cases per 1,000; ca. 80% of all shigellosis cases occurred in the first three years of life, and, among infants, shigellosis was rare until 4 months of age, when rates rose sharply. In individuals aged 60 years and above, the incidence was also shown to be high. With PCR techniques these figures are, as expected, even higher.

There is a great diversity of Shigella species and serotypes in Asia and therefore a mix of several species is needed in a useful vaccine. Surprisingly low frequencies of sequelae and deaths were found during prolonged follow up.

Today there is only one licensed (live, oral) vaccine, produced and distributed only in China. A study at ICDDR,B, Bangladesh, found an oral live Shigella vaccine candidate to be safe but non-immunogenic in that endemic setting.

Panel 1. Summary of translational research on typhoid fever and on immunization with Vi vaccine done in the DOMI Program by IVI and its partners

Is typhoid a problem?

The incidence of culture-confirmed typhoid fever (cases per 100 000 per year) was around 15–30 in China and Vietnam, around 100–200 in Indonesia and 200–600 in India (Kolkata) and Pakistan (Karachi). Moreover, the incidence was unexpectedly high in pre-school aged children in urban areas of India, Indonesia and Pakistan. Typhoid fever thus remains a public health problem and the burden of disease is high in children under 5 years of age.

Rates of multi-drug resistant *S. typhi* (resistance to the first-line drugs, chloramphenicol, ampicillin and cotrimoxizole) were found to be high in Karachi (65%) and Hue (22%), while resistance to nalidixic acid – an indicator of reduced effectiveness of ciprofloxacin and other flouroquinolones – was found in nearly 60% of isolated tested in Karachi and 44% of those in Hue. The large and growing rates of antibiotic resistance in several parts of Asia are leading to poorer treatment outcomes and higher treatment costs, thus increasing the urgency of introducing safe and effective vaccines in these areas. Conclusion: in Northeastern Asia school-based immunization would be enough but in certain areas of South and Southeast Asia infant immunization may also be necessary.

Is there a suitable vaccine?

The Vi polysaccharide vaccine was judged to be superior to the live oral Ty21a vaccine: single dose regimen, heat stable, affordable for developing world, not patent protected and technology transfer feasible allowing for local manufacturing. However, it is not effective in children < 2 yrs. Although licensed in almost 100 countries the vaccine has never been widely adopted as a routine public health tool in developing countries. Through small scale production in IVI's laboratories ways are found to give high yield and efficient processes, which then will be transferred to producers in the region (Indonesia, India, Pakistan, and Vietnam),

Is there long-term protection by the Vi polysaccharide vaccine?

Long-term follow-up of two earlier trials of Vi vaccine in China supported the notion that protection lasts for three years but failed to reveal evidence of protection thereafter. This supports recommendations for re-vaccination with Vi every three years.

Is re-injection safe and immunogenic?

A study in 1000 individuals showed no difference in clinically significant adverse events between those who were revaccinated, who got placebo or had their primary injection. The immune response was almost as good at revaccination as after primary vaccination.

Is Vi vaccine effective in controlling outbreaks?

A study in Guangxi, China showed that Vi vaccination given to students during a typhoid outbreak was 71% effective in protecting them from the disease during the outbreak, highlighting the value of Vi in controlling outbreaks, as well as in preventing endemic disease

Could mass vaccination be feasible and acceptable?

A series of demonstration projects were undertaken where populations of 5 000 to 90 000, mainly children, were immunized with the Vi vaccine. Coverage varied from 58–91%. The vaccination was found to be feasible, safe and well-accepted. Analysis of the efficacy of the vaccine is ongoing.

How can these data from individual study sites be used at the country level?

In Hue, the study site in Vietnam, the annual incidence of blood culture proven typhoid was 16 per 100 000. When adjusted for only 50% sensitivity of blood culture in detecting typhoid fever, the adjusted incidence of 33 per 100 000 now could be compared with government statistics in Hue city from the same time period. Those data underestimated the adjusted rate from the DOMI study by 13%. Assessment of incidence data of all provinces could now be done using the Government rates x 1.15. Seven provinces turned out to have high incidence (>100/100 000) and 23 provinces had medium incidence (10–100/100 000).

What about costs for disease and vaccination?

The costs of culture-confirmed hospitalized cases of typhoid found in the surveillance studies ranged from $147 in Hue to $241–$366 in Hechi, Karachi and North Jakarta and to $511 in New Delhi, India. The majority of these costs were borne by families for out-of-pocket expenses and lost wages, and represented 3.5 months of average household income in North Jakarta and nearly one month's income in Karachi. The total (government + private) costs, including both hospitalized and out-patient cases, ranged from $56 in Karachi to $139 in North Jakarta. In Hue 40% of blood culture confirmed typhoid cases were hospitalized. Mean duration of illness was 11 days. School-based Vi immunization in Hue city was found to be feasible in a DOMI project with total vaccination costs incl. delivery of US$ 1.30.

Could programs be financially sustainable without external funding or government subsidies?

Ninety percent of the cases in Vietnam are found in 22/64 provinces. If the vaccine was offered to over 15 year olds in those provinces at a price of US$ 2.10, studies in Hue has shown that the uptake rate would likely be 39%. The revenues from those adults would pay for free school based immunization in these provinces. The Viet Nam Government is now validating this form of cross-subsidization in Dien Bien province, and if successful, it is prepared to implement the program in these 22 provinces.

Among a number of other candidate Shigella vaccines, IVI is now working on a parenteral ribosomal vaccine whose initial stages of development were done at Walter Reed.

Animal tests of a vaccine based on a number of common protein antigens are at an early stage at IVI laboratories. Few laboratories have so far been interested in this type of vaccine, mainly due to technical difficulties.

Examples of translational research outside DOMI initiative

Rotavirus

Technical support is given to the Asian Rotavirus Surveillance Network (ARSN). In eight countries (China, Mongolia, South Korea, Lao PDR, Viet Nam, Indonesia, Cambodia and Sri Lanka) IVI collaborates in collecting data on disease burden, mainly from hospitals. The median value of the proportion of diarrhoeal hospitalizations due to rotavirus is 45%.

In a community based study from South Korea the risk ratio for being dehydrated was 2.9 if the diarrhoea was caused by rotavirus. The diarrhoeal death rate was investigated in nine districts in South Korea and as an example it was highest in the age group 1–3 months: 160/100 000 person years.

Two, three-year, population-based, retrospective studies of the occurrence of intussusceptions were conducted by IVI in sites in Korea and Vietnam. In the Korean site 168 patients with this condition were identified in under-five year olds, of whom 64% were infants and 81% were under the age of two years. In the Vietnam site 114 cases of intussusceptions were identified in children less than five years, of whom 64% were infants. In both sites rates of intussusceptions were comparable to those observed in the United States.

In rural China the burden of rotavirus peaks during the first 2 years of life.

The cost of treatment of rotavirus diarrhoea in urban Viet Nam is US$ 36 per case and the threshold cost per vaccine course to be cost saving in China was calculated at US$ 14.

The dominating rotavirus G-type strains in year 2006 were in Lao PDR type 1 (43%) and 3 (12%) and in Sri Lanka type 3 (30%) and 9 (26%).

Disease burden studies of rotavirus infections are planned for Kerala, India, and cost-of-illness studies in Cambodia, Indonesia, Lao PDR, Mongolia and Sri Lanka.

Phase II trials of the newly licensed, 2-dose GSK rotavirus vaccine, in collaboration with the National Institute of Hygiene and Epidemiology (NIHE), Hanoi, are ongoing in Vietnam, and a Phase III trial of the newly licensed 3-dose Merck vaccine, also in collaboration with NIHE, is about to be launched in Vietnam under sponsorship of the Rotavirus Vaccine Program at PATH (a GAVI ADIP) and Merck.

Haemophilus influenzae type b (Hib)

Doubts were raised in the mid-1990s regarding the quality of available data on Hib in Asia. Burden of disease studies (Hib as well as pneumococci) were initiated based on WHO protocols and with cooperation with WPRO/WHO, health ministries and pediatric societies in the region and UCLA School of Medicine. Staff at population-based field sites in three countries (Hanoi, Vietnam; Nanning, China; and Chonbok, Korea) was trained in epidemiology, clinical microbiology and paediatric infectious diseases; reference labs for molecular diagnosis were set up.

The annual incidence of Hib meningitis (diagnosed by culture + PCR) among under five year-old children is, however, relatively low (1–12/100 000) in these three sites. In 29% of analyzed CSF samples there was evidence of antibiotics on admission: therefore the incidence may have been underestimated if based only on culture. When compared with incidence figures from Israel 19/100 000 or Sweden 26/100 000 maybe introduction of the Hib vaccine is not necessary in these parts of Asia.

Based on the field work completed in the population-based study of invasive bacterial infections by the IVI and the National Institute of Hygiene and Epidemiology in Hanoi, Vietnam, in August 2006 the Western Pacific Regional Office of WHO commissioned the IVI to conduct a countrywide assessment of the burden of Hib disease in Vietnam, using a rapid assessment tool developed by U.S. CDC. Preliminary results show an annual Hib meningitis incidence rate of 18/100,000 in children <5 years of age. This work was presented at a national disease burden of Hib meeting held on 29 September 2006. Discussions are now underway to provide national leaders in Vietnam with complete information on the burden of Hib disease in their deliberations on whether to introduce Hib vaccine for Vietnamese children. That being said, there is today no real answer to the question whether Hib disease burden is large enough to support introduction of Hib vaccine in EPI. New Hib Disease burden studies are planned for Cambodia, Lao PDR and Myanmar.

Pneumococcus

The incidence of invasive pneumococcal meningitis in Korea, Viet Nam and China in children <5 years of age was found to be 1–2 per 100 000 per year.

Together with Harbor/UCLA clinical data from patients with pneumococcal meningitis were analysed. Case fatality rate was 19% and sequelae were observed in 32% of patients. 92% of the strains were resistant to multiple antibiotics while the vaccine would cover 71% of the reservoir.

In Nha Trang, Viet Nam, a hospital-based study started in 2005 (with support from the Pneumo ADIP at Johns Hopkins University) of invasive pneumococcal infections, i.e. including also pneumonia. The ordinary respiratory tract pathogens as well as *S. typhi* have been isolated in around 700 children with pneumonia and more than 100 with meningitis who were studied in the surveillance. In patients with meningitis 67% of urine samples were found to be positive for antibiotics.

Influenza

In general there is little information from Asia on influenza epidemiology. Simple diagnostic tests are not routinely available. A three-year retrospective analysis study of the burden of pneumonia and influenza, using Korean National Health Insurance data, is now underway. This study, conducted in collaboration with the National Health Insurance Research Center of Korea, will provide the first population-based data on epidemiologic patterns of pneumonia and influenza among children <5

years of age in Korea. These analyses will be provided to national policymakers for the further development of national influenza vaccination policy in Korea

Japanese encephalitis (JE)

In contrast to earlier reports ("Japanese encephalitis is uncommon near the equator") hospital based surveillance studies showed that JE is endemic in Bali (7/100 000 a year in children during 3 consecutive years) and also in some populations with high pig/human ratio.

Follow-up of JE patients diagnosed 1973–94 in Shanghai could show that there is a high rate of long term neurological sequelae including mental retardation and problems in activities of daily life persisting for many years. These data on disability must be accounted for when deciding on introduction of a vaccine.

Analyses imply that vaccination would be cost effective for the health systems in China, Thailand and Viet Nam and that targeted – not universal – vaccination – is highly cost-effective in Bali. Policy makers in Indonesia are in November 2006 discussing vaccination strategies based on these findings.

Japanese encephalitis has been eliminated in Japan, Korea and Taiwan by the use of the inactivated mouse brain derived vaccine, which, however, is expensive and causes adverse events. The live attenuated vaccine which is used to immunize children in China, India and Nepal is not yet WHO prequalified. There are plans to evaluate the potential for this vaccine in Indonesia while studies of disease burden and vaccine effectiveness are planned for Lao PDR, Cambodia and the Philippines.

New JE vaccines candidates will be evaluated in joint clinical programs with the manufacturers, e.g. in newly developed field sites for phase I–II trials as well as in larger efficacy trials in partnership with PDVI (see below).

Dengue

The Pediatric Dengue Vaccine Initiative (PDVI), funded by Rockefeller foundation and the Gates foundation, was recently established at IVI based on the knowledge that the disease which causes 25 000 deaths per year is primarily found in tropical countries and among children. A handful of vaccines are under development and in different phases of testing suggesting that a vaccine could be registered within 6–8 years. Partnerships exist with the public (WHO, CDC, Walter Reed etc.) as well as the private (manufacturers of vaccines and diagnostics) sector. Among activities within the program could be mentioned improvement of existing diagnostics, development of better antibody tests to measure protection after immunization and development of animal models. Today there are 5 field sites in eastern Asia and one in Nicaragua where eventually large scale clinical trials will be performed. Cost-of-illness studies are also at a planning stage.

Vaccine safety

Even when vaccines are produced according to good manufacturing practice (GMP) and tested for efficacy according to good clinical practice (GCP), it is occasionally shown that these vaccines could cause more or less severe unanticipated side-effects when introduced in national programs and used on a large scale.

Examples of proven side-effects are DTP vaccines and (HHE) hypotonic hyporesponsive episodes, OPV and paralysis and Rhesus rotavirus vaccine and intussusceptions – the latter leading to two large (n=70 000) trials of the two new rotavirus-vaccines to prove their safety.

Perhaps even more disturbing, so far mainly in the industrialized countries, is the profusion of alleged vaccine side-effects, e.g. HBV and multiple sclerosis, MMR and autism or conjugate vaccines and atopy. Examples from developing countries are DTP and increased childhood mortality in Guinea-Bissau as well as OPV and decreased fertility in some sub-Saharan areas.

Pre-licensure trials are usually not powered to detect such rare side effects – real or alleged. These studies are also done as single vaccine trials, i.e. without other vaccines or medications administered at the same time, as will happen in the normal situation. Those studies usually have a relatively short period of more intense follow up (often 42 days), which is why problems arising a long time after vaccination may not be detected. Today vaccines produced, tested and licensed in the US or Europe are given to millions of children in developing countries without real consideration given to the fact that children in those countries due to genetic or other differences may react differently to these vaccines. It must be of utmost importance in order to maintain public confidence in immunization programs that more importance is given to vaccine safety in developing countries.

In industrialized countries these real and alleged side-effects often can be evaluated through existing databases such as VAERS (Vaccine Adverse Events Reporting System) and HMO-based large-linked databases in the US. To our knowledge no such databases existed in developing countries until IVI developed one in Nha Trang, Vietnam. In cooperation with the National Institute of Hygiene and Epidemiology, Viet Nam, and funded by the Government of Japan, this project with a population size of 350 000 has collected and computerised data on immunization records, diagnoses from children hospitalized in the area as well as mortality. One first study using this dynamic database has shown that measles mass immunization is safe for children <10 yrs of age.

SWOT analysis, Translational Research and Vaccine Safety

Strengths

- Existing information and data strongly demonstrate the importance of proper vaccine safety evaluation.
- Careful choice of countries where the disease is perceived as a problem and where introduction of a vaccine can influence neighbouring countries.
- Projects conducted through already existing infrastructures (Ministries of Health or other local partners) can positively influence the decision process.
- Analysis and cost reports of disease burden are communicated to policy makers and planners.
- Cooperation with developers and producers of vaccine in developing (Viet Nam, Indonesia and Indian) as well as industrialized countries (Australia, Canada, France, Sweden, UK and the US).
- The program is strongly supported by relevant training (e.g. GCP, demography, laboratory methods) and capacity building (vaccine production according to GMP procedures and regulatory issues).
- Cooperation in field studies has started with seven countries in the Asian region and with Mozambique.
- The IVI Director-General (J.C.) is an internationally very well recognized scientist and he is also very much appreciated among the different collaborators.
- The translational research has generated an unusually large number of high impact articles published in internationally well recognized journals (see page 21).

Weaknesses

- The IVI itself is far from being located in an area where the priority diseases are prevalent, which increases the costs and limits the daily contact and collaboration between IVI and its partners.
- The different projects leaders are over-loaded with work and sometimes involved in too many tasks that delay communication between the different partners.

Opportunities

- The information gained from the translational research (i.e. disease burden and costs analysis and effectiveness of vaccinations) will help the policy makers in their decisions whether the country should introduce a new vaccine or not.

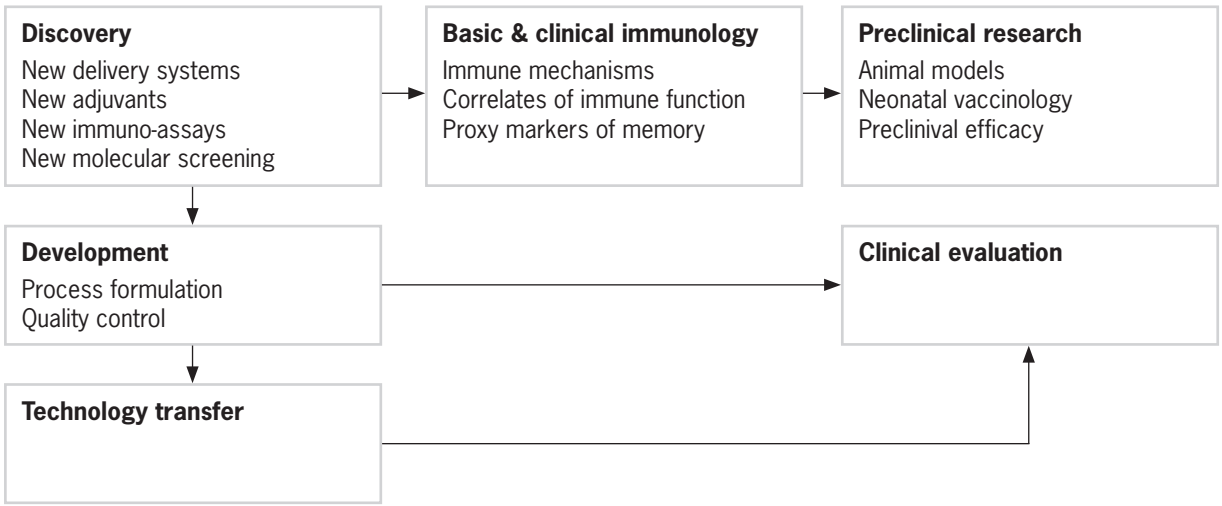
- The new vaccines will decrease the disease burden and thereby improving health and survival, especially of small children.
- The production of FDA and/or WHO approved vaccines locally will improve availability and distribution of vaccines to countries in need.
- These new companies in low- and middle-income countries will fill the void seen today when companies in industrialised countries are leaving the production of vaccines tailored to developing countries.
- The vaccination sites and the IVI activities in general will generate training for young health professionals both from developing and developed countries.
- The successful field activity on vaccine safety established in Viet Nam could be replicated elsewhere, preferably in Africa, and maybe in collaboration with well-functioning health and demographic surveillance sites (e.g. those within the INDEPTH network).

Threats

- Too little funding and personnel to cope both with the expansion of sites and continents as well as vaccines.
- The collaborating sites and countries will become more and more independent, potentially limiting the need for collaboration with IVI, unless the collaboration further develops into an equal partnership with well-defined roles.
- Donors might lose their interest in IVI and instead support similar activities in the different countries directly, or through other international actors in the field of vaccines.
- The disease priorities among policy makers might move towards problems related to diseases now even seen in the developing world (i.e. obesity, autoimmune diseases, cardiovascular diseases and cancer).

Laboratory research and vaccine development

The laboratory research at IVI started in 2004. As can be seen in the Figure below the laboratory research covers research areas from new discoveries to basic and clinical immunology, preclinical research and to clinical evaluations.



The overall aim of the Laboratory Science division is to strengthen IVI's overall contribution to vaccine development. To reassure this, the division works in close collaboration with the Translational Research Division in molecular epidemiology and laboratory follow-up of vaccine trials. The Laboratory Science is equipped with state-of-the-art equipment and will during the spring 2007 get a combined (animal/clinical) high security containment facility (BSL3+) for conducting pre-clinical and clinical studies on dangerous pathogens such as pandemic influenza viruses, SARS, HIV and *Mycobacterium tuberculosis.*

The Laboratory Science Division comprises three main departments: 1) The Department of Immunology with sections of Mucosal Immunology and Clinical Immunology; 2) The Department of Microbiology with sections of Molecular Microbiology, Bioinformatics and Molecular Vaccinology and 3) The Department of Vaccine Process, with sections of Process and Quality control, and Conjugate Vaccine Production.

Department of Immunology: Mucosal Immunology Program

Alternatives to parenteral administration of vaccines include mucosal vaccination, since this route of administration eliminates the need for needles, which, if not properly sterilised, could transmit blood-borne infections. Several vaccines already exist that are given via the mucosal route (i.e. cholera, rotavirus and polio). To improve these and other vaccines it is essential to better understand the mucosal immune responses. The Mucosal Immunology Program is involved in research aiming at characterising optimal vaccination routes for tissue-directed immunity. Several new administration routes are presently tested out in murine experimental models (nasal, buccal and rectal), which are compared to systemic (intradermal and transcutaneous) delivery routes. Detailed analysis and comparisons of the cellular and molecular mechanisms induced by the different vaccines in the mucosal tissues as well as systemic responses are conducted. Promising data have been obtained using sublingual administration of murine influenza and efforts are now being made to improve this administration route using different liquid- or semi-liquid formulations. During the last year the group also has developed a guinea pig model for *Shigella*-induced enterocolitis which mimics the pathology seen in the human form of the disease.

Department of Immunology: Clinical Immunology Program

The clinical immunology program is developing and standardising assays for measuring vaccine-induced human B and T-cell responses; especially assays that require small amounts of blood and less sophisticated equipment making them better adapted for use in developing countries. The program is also involved in the establishment of a reference laboratory for the standardisation and validation of assays for typing of pathogens. Such assays are already available for *V.cholerae, S.pneumoniae,* and *S. typhi.*

Department of Microbiology; Molecular Microbiology and Bioinformatics

Bacterial pathogens such as *Salmonella, Shigella, Vibrio cholerae* and meningococci are genotypically diverse. The pathogens can change their genetic set up by horizontal genetic exchange that can change the virulence of the pathogens. This might have important implications for vaccine development.
A database is presently built up at IVI where all data obtained from the genomic screening of the pathogens (i.e. ribotyping and multilocus sequence typing, MLT) are stored. The MLT system has recently been used to analyse isolates from a recent cholera outbreak in Mozambique and all strains were shown to belong to a common but unique strain. IVI is also in the process of developing a user-friendly interface for a variety of bioinformatics analyses, such as clustering and ordination methods.

The already established methods and analyses will also be transferred to the new pathogens to be studied at IVI (influenza virus, *M.tuberculosis, S. pneumoniae,* SARS).

Department of Molecular Microbiology: Molecular Vaccinology Program

The major objectives of the Molecular Vaccinology program are to develop a generic strategy for identifying protective antigens and/or defined moieties thereof against a panel of enteric bacterial

pathogens *(Salmonella, Shigella,* and *Vibrio cholerae)* as well as of certain respiratory pathogens (Influenza virus, *M.tuberculosis, S. pneumoniae,* SARS). In addition, the unit is also involved in the development of vectors and new adjuvant for the optimal delivery of vaccines.

So far the vaccine discovery activities of this unit have mainly focused on DNA vaccines and on identification of common outer membrane proteins that might serve as simplified vaccines against *Shigella* IVI scientists have identified several surface expressed and secreted *Shigella* proteins that will be evaluated as new vaccine candidates in murine experimental models for human shigellosis. A program on influenza vaccines will commence next year.

SWOT analysis, Laboratory Research

Strengths

- The Laboratory Research uses state-of- the art techniques with the aim to answer questions relevant for the next generation of vaccines, which hopefully will be administered through the mucosal route.
- A new guinea-pig model that mimics the pathology seen in humans infected with *Shigella* will be very useful for the understanding of the molecular mechanisms of the pathogenesis of this disease, of importance for future vaccine development, and will serve as an improved animal model for evaluating new vaccine constructs
- The Laboratory Research work both with animal experimental systems and with humans.
- For the human studies the program is optimising all assays so that they can be used under less developed conditions and with small blood volumes.
- The data base to be used for storing genomic data from all the different pathogens will not only be useful for IVI itself but also for the rest of the world.

Weaknesses

- With the limited numbers of personnel it is essential that IVI attracts senior staff with appropriate competences (post-doctoral fellows or senior scientists).
- The population exposed to the targeted diseases is far away, and the collection of appropriate biological samples may be cumbersome. This complicates the ambition to do appropriate basic research related to IVI's mandate.

Opportunities

- The development of technologies requiring small blood volumes and less sophisticated equipment may, together with the network of well functioning field sites, offer golden opportunities for relevant and cutting-edge research on different pathogens.
- There is an opportunity to develop state-of-the art laboratory research in collaboration with some of the current partners in countries where target diseases are prevalent and patients are at hand. IVI's partners in Kolkata and Dhaka have competent staff and sophisticated laboratories that could offer such opportunities. The newly discovered *Shigella* surface expressed and secreted antigens are very promising new vaccine candidate antigens and should be rapidly evaluated.

Threats

- There is a risk that the laboratory research priorities are less relevant in relation to the overall mission of the institute.
- Too many research questions and smaller projects could also create a loss of focus.

The Department of Vaccine Process, with Sections of Process and Quality control, and Conjugate Vaccine Production

The vaccine process laboratory at the IVI focuses on improvement of the manufacturing process on a laboratory scale. When fully developed IVI will transfer the manufacturing process and facilitate the up-scaling and quality control of the product. IVI will also transfer serological assays and be involved in the clinical trials needed to validate the vaccines.

During the last two years IVI has been assisting one of the Vietnamese vaccine manufacturers, VABIO-TECH, to improve the quality of their oral cholera vaccines up to WHO standards. This has resulted in reformulation of the vaccine to eliminate a toxin-producing strain. This new formulation has been used in phase II clinical trials in Vietnam and in an endemic setting in Kolkata, India. The results showed that the new formulation was superior to the former with regard to immunogenicity and safety. In addition to this vaccine IVI is also in the process of technology transfer of this reformulated cholera inactivated whole cell vaccine to the vaccine producers in India and Indonesia.

Several lots of Vi polysaccharide vaccine against typhoid fever have been produced and quality assured. The purified Vi has been tested for immunogenicity in mice and been shown to induce good responses. The extraction protocol has been improved but further improvements are still needed. In addition, the IVI has established collaboration with Dr. John Robbins' laboratory at U.S. NIH on development at laboratory scale of a Vi-DT conjugate vaccine. The IVI group has developed a process that produces Vi-DT at high yields and with acceptable reproducibility. Assays have been validated and standard reagents produced to support clinical trials of Vi and ViDT-conjugate typhoid vaccines. Both vaccines will be transferred to emerging vaccine producers in the near future.

A protocol has been developed for the purification of ribosomes from *Shigella* bacteria, in a program designed to follow up on a promising vaccine development program at Walter Reed Medical Research Center. Safety and immunogenicity studies in mice have shown promising results. However, the constructs showed a large batch-to-batch variation and also contained LPS. A possible solution could be to use a detoxified mutant to prepare the ribosomes.

Technical Assistance and Technology Transfer Program

The major aims of this program are to provide training of health professionals in developing countries in disciplines related to vaccine research and introduction (clinical microbiology, immunomonitoring, epidemiology, computerized data management, clinical trials, economic research, sociobehavioral research, and policy analysis), and to ensure that suitable vaccine technologies are transferred to the manufacturers in the developing countries and that the manufacturers will follow appropriate national regulatory standards. IVI assists in this by training the local people in production, quality control and regulatory requirements. The training of the local producers is given in a sandwich program including training at IVI and at their home institutions with the help of IVI facilitators. This has already taken place with the inactivated whole cell cholera vaccine with which clinical studies presently are undertaken in Viet Nam and India (phase II and III trials).

In addition to "training by doing" IVI has for the past six years jointly with the London School of Hygiene and Tropical Medicine been running a number of annual courses for professionals in developing countries in vaccinology. In 2006, IVI hosted its sixth Annual Advanced Vaccinology course for the Asia-Pacific Region at the IVI headquarters building. The week-long course was sponsored by the Bill and Melinda Gates Foundation, the Government of Kuwait, the Swedish International Development Cooperation Agency (Sida), GlaxoSmithKline (GSK), and Sartorius. The course aims at strengthening the overall vaccinology capacity of countries from the Asia-Pacific regions by providing participants with a comprehensive overview of the vaccine continuum, from vaccine development, evaluation,

regulatory, and ethical principles, to production, introduction, and policy issues. In 2006 a total of 51 attendees from 19 different countries including Bangladesh, Brunei, Cambodia, China, India, Indonesia, Korea, Lao PDR, Malaysia, Mongolia, Nepal, Pakistan, Philippines, Singapore, Sri Lanka, Taiwan, Thailand, Turkey, and Viet Nam, actively participated in the course. Fifteen scholarships are awarded each year to senior professionals from the developing world, following a rigorous selection process by an independent scientific advisory committee.

Annex 4 shows the agenda of the course. The course is structured as a series of didactic presentations and practical exercises based on specific aspects including immunobiology, vaccine development and production, clinical evaluation, regulatory and ethical issues, post licensure trials, introduction strategies and policy. In addition the course has round table discussions addressing relevant topics such as vaccine safety or alternative regulatory strategies for developing and developed country markets. The round-table discussions provide participants with the opportunity to ask experts about specific questions related to their own work experience in their home countries.

A workshop on Clinical Trial Design, Monitoring and Evaluation was held at the IVI Headquarters in Seoul September 12–16, 2006. This workshop was sponsored by USAID, the Developing Country Vaccine Manufactures Network (DCVMN), and was targeted to members of the DCVMN. Manufacturers from Brazil, China, India, Indonesia, Viet Nam and South Africa sent representatives from the clinical development side or medical divisions to attend the workshop.

The workshop aimed at providing the participants with technical tools and background to prepare satisfactory protocols of well designed trials, to conduct the trials in accordance with Good Clinical Practice (GCP) to conduct appropriate analysis of the trials, and to prepare suitable dossiers on trials for regulatory review. At the request of the DCVMN, the workshop focused mainly on the combination vaccines using DTP as a base, such as DTP+Hep B, DTP+Hib and DTP+Hep B+ Hib, since several emerging producers are engaged in the clinical development of such combination vaccines and since GAVI also has indicated interest in purchasing a pentavalent vaccine if all requirements for WHO prequalification are meet.

The workshop consisted of theoretical and practical lectures and case studies. Clinical protocols for combination vaccines were sent from a number of local manufacturers to the IVI and lectures and case studies from the workshop were tailor-made to reflect the most commonly mistakes both in the field and as well as in the protocols.

SWOT analysis, Department of Vaccine Process, and the Technical Assistance and Technology Transfer Program

Strengths

- The Department of Vaccine Process has shown that they have a great expertise in optimising the vaccine production process and quality control.
- The Program has shown very good collaboration with the vaccine manufacturers in Viet Nam, India, and Indonesia which facilitates the transfer of technology.
- The Program has clearly shown that they have the capacity to transfer all technologies needed for the development of GMP-produced vaccines to the local manufacturers.
- The Program has conducted a broad array of training activities of value to vaccine professionals in developing countries.

Weaknesses

- The ribosomal Shigella vaccine which contains LPS should have a very low priority if the LPS and batch to batch variation can not be solved.

Opportunities

- The IVI model of technology transfer for vaccine production and training is a unique possibility for IVI to show the world that it is possible to develop cheap, safe vaccines with good efficacy using local manufacturers.

Threats

- Too many new vaccines that need process development are introduced and the work load of the existing personnel and production equipment may be too high.
- Other organizations might take up the idea and challenge the uniqueness of IVI.
- Transfer of technologies can be slowed down by working with local vaccine producers who are not yet producing vaccines at international quality and by administrative clearances required by partner countries

Cross-cutting issues

Overall achievements and results

Since its start IVI has gradually established major research programs in 21 countries in Asia, Africa and South America. IVI has shown that it fills a unique niche in global efforts of vaccine research, development, training and technical assistance. The success of IVI is linked to its successful collaboration with universities, Ministries of Health, local biotechnology companies, WHO, and vaccine developers in both industrialised and developing countries. IVI works both down stream to accelerate the development and rational introduction of new vaccines as well as up stream to speed up the discovery and development of new and improved vaccines for the world's poor populations.

IVI is well on track with its mission – among other things reflected by the numerous internationally published articles where the majority of articles are related to translational research.

Publications

A large number of publications from IVI and its partners reflect high productivity. The table below presents research area (translational research or other) and country of origin of first author, and covers publications January 2005 up to November 2006. Productivity is high and translational research dominates the list.

Type of research	Country of origin, first author											Total
	IVI	Pakistan	Bangladesh	China	Korea	Vietnam	Indonesia	Sweden	France	USA	Other	
Translational	28	4	2	6	2	5	6	0	1	6	5	65
Other	16	0	1	6	11	0	0	2	3	8	3	50
Total	44	4	3	12	13	5	6	2	4	14	8	115

Organisation, funding and budget

The activities of IVI are governed by an international Board of Trustees with 22 members, where the majority of members are chosen in their individual capacities. The board has various committees – Executive, Finance and Facilities. The Executive Committee meets once a year between the regular annual Board meetings. The Chair is currently coming from Sweden (Ragnar Norrby).

In addition a Scientific Advisory Group (SAG) has been appointed representing expertise needed for proper guidance of IVI's scientific activities. The SAG meets annually, just before the annual Board

meeting, to review the institute's scientific accomplishments and plans. It reports it's appraisal of the Institute's scientific program at the annual Board meeting.

The IVI's operation is led by a Director General (John Clemens), who heads a senior management team comprised of the Deputy Director General for Research Coordination, Programs and Institutional Development (Luis Jodar), Deputy Director General for Administration and Finance (Michael Goon), Deputy Director General for Laboratory Sciences (Cecil Czerkinsky), and Deputy Director General for the Pediatric Vaccine Initiative (Harold Margolis).

The decision about the introduction of new vaccine research programs and new opportunities for strengthening IVI's capacities are decided by the Executive Board in close collaboration with the Director General, the Deputy Director Generals, and the Scientific Advisory Group.

Before starting a new vaccine development program a careful analysis of the disease burden and cost benefit for the patient and country is done in close collaboration with local vaccine producers, health workers and the Ministry of Health. All projects are reviewed by National Ethical Committees as well as the Institutional Review Board of the IVI, which is registered with the U.S. Office for Protection of Human Subjects.

The IVI annual budget has gradually increased since its establishment in 1997. For 2007 IVI's budget is projected at USD 25.4 million. Very few donors (the Korean Government, Sida, Sweden, and Kuwait Government) give core contributions to help support the laboratory programs as well as costs of utilities, maintenance etc. Other countries, where IVI has projects, give support with e.g. manpower to facilitate the work.

Budget projections 2007 (US$)

Republic of Korea (ROK)	4,530,000
Sida, Sweden	360,000
Sartorius	100,000
Kuwait	50,000
KSC/Funding in Korea	750,000
Biomax	175,000
Gates Foundation	17,046,257
Other restricted	1,150,000
Interest income	500,000
Other income	790,000
Total income	25,451,257

The majority of donors like Gates foundation, PATH, UBS Foundation and KOICA support only specific projects and then mainly within the program of translational research.

ROK has over the years given strong economical support; in the beginning providing a major fraction of IVI's total budget and in 2007 providing nearly 20% of the total budget.

ROK has also generously donated the headquarter building as well as funds to equip the laboratories.

The major activity within IVI is translational research and thus corresponding to the major part of funding, USD 17.7 millions, is allocated for these activities in 2007. Within that program the Typhoid and Cholera Vaccine research programs have been dominating over the years. However, during the

period 2000–2006 the major dengue research program constituted approximately one quarter of the expenditures.

The signatory countries do not have to provide annual fees. The list of signatories is dominated by low- and middle-income countries. The exceptions are Sweden, the Netherlands, Korea, Kuwait, Spain, the United Arab Emirates, and Oman.

IVI is classified as a public charity under Section 501 (C) (3) of the United States Internal Revenue Code, as it gets a substantial part of its support from a governmental unit or the general public. It is thereby given a favourable taxation but it is important to keep and – if possible – increase this "public support" to avoid being seen as a private foundation with higher taxation on funds received from the United States.

In an evaluation during the autumn of 2005 sponsored by the Gates foundation to evaluate IVI's handling of their grants, it was stated that IVI "…appears to have adequate financial and programmatic management capacity…" and appears "…effective in implementing and controlling projects as designed".

IVI in the global landscape

How does the IVI specifically complement the activities of other major public-sector players in the realm of vaccines for developing countries?

1. GAVI Alliance

   The GAVI Alliance is devoted to improved delivery of routine childhood vaccines. For research on new vaccines GAVI relies on its technical partners (GAVI does not have in–house research expertise). GAVI's research activities are time-limited projects devoted to accelerated introduction of a single vaccine or vaccines against a single disease. These projects tend to operate as virtual entities with small coordinating secretariats at GAVI's partner organisations (e.g., JHU, PATH), relying on outside partners to undertake technical activities. IVI is a technical organisation that undertakes research for these GAVI initiatives (the IVI currently conducts research commissioned by the pneumococal and rotavirus ADIPs, as well as the Hib Initiative). IVI also has the capacity to host these initiatives.

2. WHO

   WHO is the world's premiere international organisation for setting policies on vaccines for developing countries. WHO also supports research, and sponsors a great deal of training. For its policy setting activities WHO relies upon research conducted by outside technical organisations and also relies upon the advice of technical experts. IVI conducts this needed research, and IVI scientists serve on WHO expert committees that provide recommendations on policy. For research on new-generation vaccines, WHO funds outside organisations to conduct the research. IVI is one such organisation. Likewise, in its training activities, WHO relies on its technical collaborators, such as IVI. An example is IVI's role as an implementing organisation for WHO's Global Training Network for vaccine manufacturers. Finally, in contrast to WHO, which has legal restrictions on working with industry, IVI has very few restrictions, and it is therefore able to undertake collaborations with industry, including transfer of vaccine production technologies to emerging producers, which are needed in many programs of accelerated vaccine development and introduction for developing countries.

3. UNICEF

   UNICEF is the world's leading international organisation encharged with procurement and delivery of routine immunisations for children in developing countries. UNICEF is not a research organization. IVI's research helps generate the evidence that UNICEF needs in decisions about which new generation vaccines to include in programs in developing countries.

4. Gates Foundation-Supported Initiatives (e.g., Malaria Vaccine Initiative, Meningococcal Vaccine Program, Aeras (tuberculosis vaccines), Hookworm Vaccine Program)

   These are initiatives devoted to accelerate the development and/or introduction of vaccines for developing countries. Each initiative has a focus on a single disease, and at times a single vaccine. The initiatives are not created as permanent organisations, but as time limited projects, usually within larger permanent organisations, such as PATH. The activities of these initiatives focus primarily on product development. These initiatives often function as "virtual" organizations, outsourcing technical activities to technical organisations such as the IVI. They do not focus to any appreciable degree on capacity-building. In contrast, the IVI is a permanent, international organisation, with a broad array of research activities throughout the vaccine continuum, from discovery to introduction, undertaken by IVI's own scientists. Moreover, the IVI focuses on vaccines against multiple diseases of public health importance to the developing world, and carries out research on cross-cutting themes of importance to vaccines for developing countries, such as vaccine safety. Finally, the IVI undertakes a wide variety of training and capacity-building activities of importance to vaccine development, production, evaluation, introduction, and use in developing countries.

5. Government scientific organisations and universities

   Many of these organisations are capable of conducting excellent research on specific aspects of vaccine discovery and evaluation. They usually do not have the capability to develop their discoveries into products. They typically do not focus on capacity-building. Moreover, while many of these organisations conduct research within developing countries, they do not have the legal legitimacy of international organisations. IVI, which has expertise in applied vaccine development and has an extensive network of collaborating vaccine manufacturers in the developing world, works with government scientific organisations and universities to translate scientific discoveries and prototypes into products, and to facilitate clinical research programs on these products leading to licensure. Its status as an legally constituted international organisation enhances the effectiveness of IVI in these collaborations, as does IVI's ability to merge capacity-building with research activities in these projects.

SWOT analysis, cross-cutting issues

Strengths

- IVI is well on track in developing its unique mandate and working philosophy.
- IVI has a well functioning organization and has been successful in getting sufficient funding for running its operations and growth.
- The Korean government has generously supported the institute.

Weaknesses

- IVI is mainly focusing its activities in Asian countries.
- Sustainability of funding is critical for the future of IVI; the dominating role of one major donor is problematic.
- Intellectual property rights issues, authorship of publications etc. are sometimes unclear in the relation to collaborating institutions in low-income countries.
- Several countries with shown interest in vaccine issues (e.g. GAVI supporters) are missing in the list of signatories.

Opportunities

- An expansion of IVI's activities to new geographical areas (Africa, Latin America) could also be reflected in an increase in number of signatory countries and improved geographical representation in the Board.

- The establishment of a policy unit could further strengthen IVI's unique role in translation research and search for sustainability in vaccine programs.

Threats

- There is a risk that IVI is too ambitious in its ambitions and that IVI thereby will loose its focus
- There is a risk that IVI is taking on too many new projects and that donors will not sustain their funding.

Evaluative conclusions and recommendations

General conclusions and recommendations

IVI has shown impressive growth and is well on track in relation to its stated mission and aims. The contributions in translational research and training are especially impressive and the contributions to the vaccine area are very relevant. IVI appears effective in implementing and controlling projects as designed. It has today exerted major impact on policy decisions about vaccine development and introduction for a number of diseases. This is an area where further geographical expansion is recommended. So far most of IVI's activities have been largely focused on a number of Asian countries. Many of the global challenges are found in Africa, where IVI's niche and special competence could be of great value in addition to the major investments done by GAVI and other international actors.

IVI has entered into an exciting phase of its development. Its future growth will capitalise on its strengths and on the niche that it already established by virtue of its demonstrated capabilities in translational research and training, and its rapidly growing activities in vaccine development and laboratory sciences. Its growth will be phased and strategic to accommodate the realities of funding, recruitment and geographical expansion.

Considering the special role and capacity of IVI and the vast number of vaccines currently included in its portfolio we presently recommend a geographical expansion (within Asia as well as elsewhere, i.e. Africa and South America) rather than an increase in number of vaccines included in its portfolio. The establishment of a policy unit should be a useful mechanism in a geographical expansion of the translational work activities, and further improve the communication with policy makers and planners.

IVI should continue to assist by providing the necessary expertise and knowledge in product development, assay development, challenge models and protocol harmonisations across the different sites.

IVI is already involved in numerous Molecular Biology and Laboratory Science projects. There is a need to trim down the number of these projects, with priority given to those of immediate relevance for translational research. It is essential that the Vaccine Process Research Program gets the prioritised vaccines to the field, in close collaboration with national scientists, thereby generating success stories of local production of vaccines according to GMP for populations in need.

We also strongly support the development of an additional vaccine safety unit as already done by IVI in Viet Nam. This new safety unit should preferably be established in Africa, maybe in collaboration with one or a few of the health and demographic surveillance sites that exist within the INDEPTH network.

IVI shows an impressive expansion in total funding. However, most funds are linked to specific projects, and few donors provide core funding. Further, one major donor has a dominating role that could threaten sustainability of the institute and its activities. An increased number of financially supporting

partners that preferably provide core support to IVI would prevent the financial fluctuations and risks that a dominance of project funding implies; it would allow the organisation to pursue its tasks in a sustainable way, and would also allow the organisation to enter into new and prioritised areas where international funding is unavailable. The number of member states needs to be increased, and membership should preferably be linked to long-term financial contributions. This is an important issue for the Board but also for the current signatories. As visible results are important for the major donors in their decision-making process, it is of paramount importance that IVI can provide a clear description of their processes and concrete deliverables with regard to its specific objectives.

IVI is unique

As repeatedly stated above, IVI gives a unique contribution to the international vaccine arena. In order to increase its visibility, attract funding and further develop collaborative advantages IVI should strengthen its collaboration with GAVI and other major actors in the international field of vaccines. Good progress in this area has been made in the past year, with the creation of an ex officio seat for the GAVI Alliance on the IVI Board of Trustees (WHO already has two ex officio seats on the Board), and with the election of the IVI Director General to a seat on the GAVI Alliance Board. Likewise, the IVI has established multiple collaborations with WHO at the headquarters and regional levels.

What is then the unique contribution by IVI among the many actors on the international arena? The IVI is the world's only international research and development organisation devoted exclusively to new vaccines for developing countries. Apart from its mission, this uniqueness derives from several features:

- It is a legally constituted international organisation under the Vienna Treaty, currently with 39 countries and the WHO as signatories. This international character gives the IVI an international legal legitimacy that is shared by few other organisations and that is at times crucial for its work in developing countries.
- It is a technical organisation with in-house capabilities spanning the entire vaccine continuum, including basic vaccine discovery; applied immunology, including development of improved immuno-monitoring assays for use in developing countries; molecular microbiology and bioinformatics, including genetic characterization of field isolates for molecular epidemiology studies; applied vaccine development and process laboratories, devoted to improved production techniques and technology transfer; clinical trials; epidemiological studies; socio-behavioural studies; economic studies and analyses; and policy analyses. While some multinational vaccine producers have this range of in-house technical expertise, such companies do not focus on poor populations in developing countries and few if any organizations in the public sector devoted to vaccines for developing countries have this breadth of technical research expertise.
- The IVI has created integrated networks of collaborators including other international organisations, such as WHO and the ICDDR,B; institutions in developing countries; universities and government scientific institutions, and other technical organisations in the industrialised world; and industry in both industrialized and developing countries, which have allowed the IVI to create unique programs of research, capacity-building, and technology transfer related to the introduction of new vaccines for developing countries, such as the DOMI Program.
- The IVI has major programs on capacity-building for professionals in the vaccine sciences in developing countries. No other public sector organization in the vaccine arena combines broad research programs with such extensive training activities.
- An area of capacity-building that warrants special comment is IVI's activities in technology transfer of vaccine production to emerging producers. Accordingly, the IVI is regularly cited by the Developing Country Vaccine Manufacturers Network (DCVMN) as a major resource for its members.

Internationalisation

So far IVI activities mainly have focused primarily on Asia. Many of these countries are more developed compared to countries on the African continent. The introduction of the IVI research philosophy into the African continent is strongly warranted. The way to introduce IVI in Africa could be done by running workshops and courses in selected African countries. This should preferably be done together with the African Union (AU). This would give IVI a possibility to get a feeling where it would be possible for IVI to promote the development and introduction of new and improved vaccines to relieve the burden of the infectious diseases IVI is focusing on and which is a great problem also in Africa. IVI's programs on policy and economic analysis of different disease burdens will potentially influence professionals and decision makers who are responsible for the design and implementation of health care systems. It is important that this process is initiated. However, since the challenges working in Africa are very different from working in Asia IVI needs to collaborate closely with organizations such as African Union and EDCTP (European & Developing Countries Clinical Trials Partners), where the latter would be a natural link to EU.

Establishing a policy unit

The fundamental question of the role of IVI (co-ordinating body, vaccine developing- capacity building, research or funding organisation or a mixture of some or all of these) needs to be addressed. There are many more players now in the field of addressing issues related to development and use of vaccines for people in developing countries. In order for IVI to focus its attention on its primary objective there is a need for IVI to focus on certain aspects and then concentrate on areas where they so far has been extremely successful. We feel that a focus on a policy making unit will strengthen IVI's present role among all present vaccine initiative players. This unit will make it possible to transfer the technologies needed to new study sites not only in Asia but also in Africa and South America where there is a great need for similar analysis. IVI would thereby take an international leading role for the co-ordination, capacity building and training in this.

The roles of the unit would include: 1) undertake methodological research to develop simple, inexpensive tools to obtain data needed for analyses of alternative vaccine and non-vaccine control options for targeted diseases and obtain appropriate estimates of disease burden at the country level; 2) develop improved analytic methods for comparing vaccine and non-vaccine options for disease control, including creation of user-friendly tools to communicate these analyses to policymakers in an understandable fashion; and 3) service as an "honest broker" consultant to developing countries that request external assistance in obtaining and analyzing evidence on options for vaccine introduction.

This policy unit should be co-ordinated by IVI. The mission should be clearly communicated to the outside world. IVI should state this vision in its strategic plan. With this policy unit IVI would get a role as a country support team which would help the individual country decision makers as well as GAVI and other vaccine initiative organisations to decide whether they should introduce new vaccines or not.

The donors and board should take a clear decision to support this policy unit, a decision that will have implications with regard to the budgetary and human resources that IVI needs.

Recommendations to Sida

The greatest success of IVI so far has been its involvement in and development of the Translational Research Program. This is a unique niche for IVI, with contributions of outmost importance for bridging the gap in health between high and low income countries. Other major actors within the vaccine area, e.g. GAVI, focus on the procurement and distribution of vaccines. IVI's program adds sustainability to these efforts.

Based on the evaluation of IVI, its role and achievements and potential for the future we propose an increased core support from Sida/SAREC for the forthcoming agreement period starting in 2008. A suggested level of support could to be 15 million SEK per year during the next agreement period.

Sida/SAREC is also recommended to assist IVI in identifying and stimulating additional member states and long-term financial contributions. By providing long-term core support Sida sets a standard that could be repeated by other signatories. It is logical that membership also implies financial commitment.

Annex 1, Terms of Reference for the evaluation of the International Vaccine Institute (IVI) to be done 2006

Background

In June 1992, United Nations Development Program (UNDP) initiated the process of creating IVI since UNDP believed there was a need for an international non-profit organisation that would be a catalyst in addressing issues related to development and use of vaccines for people in developing countries. Following a detailed feasibility study and a competition among the Asian countries to be the host, IVI was established on the campus of Seoul National University in the Republic of Korea (ROK) as an autonomous international organisation under the Vienna convention of 1969. The institute began operations in October 1997. ROK made a commitment to provide 30% of the annual budget. However, local economic problems the first years of IVI's existence made it difficult to meet this obligation and this caused a delay in the laboratory activities of IVI. In addition, project funding has grown at the IVI more rapidly than projected. It currently has 37 signatories: 36 countries and the WHO. Sweden is one of the signatory countries and has been so since IVI's inception.

The mission is *"The IVI will contribute to reduction of disease caused by vaccine preventable diseases in developing countries by collaborative research to generate the evidence needed for rational introduction of new vaccines, supported by programs of basic and applied laboratory research, product development, training and technical assistance".*

IVI give priority to vaccines against diseases of importance in developing countries. These are: cholera, shigellosis and typhoid fever (diseases of the most impoverished, DOMI), Japanese encephalitis, *Haemophilus influenzae* type b, *Streptococcus pneumoniae, Neisseriae meningitides,* rotavirus, dengue and enterotoxigenic *Escherichia coli.*

Activities of the IVI focus on filling major gaps that exist in strategic research, laboratory research, product development, technical support and capacity building for vaccines of priority concern to developing countries. IVI's in-house expertise provides it with a strong basis to assist in training programs to strengthen scientific, production quality control and regulatory skills in developing country institutions to accelerate the introduction of vaccines in poor countries. Examples of programs are clinical evaluation of vaccines and postdoctoral training at selected centres in developed countries.

Since the inception of the institute it has been evaluated once in its early stages of implementation (2000), an evaluation commissioned by UNDP. Many of the recommendations were linked to IVI's relationship with UNDP e.g. it recommended a continued UNDP commitment, both morally and financially. However, because of changing priorities at the UNDP, it no longer provides core support to IVI. Other recommendations were that cooperation and communication between IVI and GAVI should be continued and expanded in well-defined areas, that IVI should strive to develop itself into a fully international institution and that future research efforts of the IVI should be closely linked to its ongoing activities in epidemiological field studies of disease burden and vaccine effectiveness. Further, IVI was recommended to communicate more effectively its existence, mandate and mission to developing countries, to private industry and donors. Finally, in recognition of its status as an independent international institute, IVI should ensure continued external review of its future activities to ensure objectivity and transparency.

Sida/SAREC has supported IVI since 2002 and has since then contributed with 12 MSEK. The ongoing agreement covers 2005–2007. The reason why Sida is commissioning an external evaluation is partly because this was requested by Sida's Research Committee in February 2005 as a precondition for continued and perhaps increased support and thus the current agreement includes an evaluation to be

made during 2006. Secondly, it is Sida's policy to regularly evaluate the organisations receiving support from Sida. Thirdly, given that there are so many new actors in the field of vaccine research, it is considered by Sida to be very timely to evaluate IVI.

Purpose and scope of the evaluation:
The purpose of the evaluation is to assess the relevance, efficiency, effectiveness and impact of IVI in relation to its stated mission and functional structures and operating environment from 2000 until now and also in the future. The scope of the evaluation is to focus on future direction and management of the programs resulting in concrete and realistic recommendations, especially regarding program activities, interaction/collaboration with other key stakeholders in the area of vaccine research.

Programs to evaluate
The disease focus of the evaluation will be on *diarrhoeal diseases,* i.e. DOMI (i.e. cholera, shigellosis and typhoid) and rotavirus, and on *respiratory diseases,* i.e. bacterial meningitis, pneumonia. In addition, Japanese encephalitis and dengue will be included. The programs to be included in the evaluation are:

- *Translational research,* e.g. burden of disease studies, clinical studies of experimental vaccines, cost-effectiveness studies, policy studies
- *Vaccine safety*
- *Laboratory research (start 2004)*
- *Vaccine development and process research,* e.g. the manufacture of a Shigella ribosomal vaccine prototype
- *Technical assistance and training,* e.g. training in vaccine production and regulation, training in GCP, training in vaccinology and advanced laboratory techniques

The assignment (issues to be covered by the evaluation)
The consultants should evaluate the following:

Achievements in relation to its mission and the continued relevance

- Assess IVI's national, regional and global achievements* since 2000 including the possible direct and indirect effects and impacts
- In what way is IVI contributing to the UN Millennium Development Goals?
- Assess the likelihood that IVI will contribute to global public goods
- Assess and make recommendations on the continued relevance of IVI including its mission and vision and strategies considering the changes in the external environment that have been taking place the last years with increased number of players in the field of vaccine research
- Based on above information, reflect on the comparative advantages of IVI in relation to other partners and provide some inputs for the way forward to enhance future relevance and performance

Achievements/results

- Effectiveness – The extent to which IVI's objectives have been achieved or will in the future – is the program on track?
- Impact – what are the overall effects of the program
- Relevance – the extent to which the objectives of IVI are consistent with the national, regional and global needs.
- Efficiency – the extent to which the costs of the activities can be justified by the results.

Collaboration/Cooperation

- To what extent is IVI collaborating/cooperating with international organisations such as WHO, UNDP, GAVI and ICDDR,B.
- In what way is IVI collaborating with MoH in the target countries
- In what way is IVI collaborating with the private industry in developed countries?
- In what way is IVI collaborating with the private industry in developing countries?
- Give concrete recommendations on how collaboration/cooperation with above mentioned key stakeholders could be enhanced.

Organisational and funding issues

- Describe the management structures including review and ethical committees at IVI for deciding on what projects to support and which research areas, diseases and countries to engage in.
- What are the strengths, weaknesses, opportunities and threats to the IVI activities. A use of a SWOT analyses is recommended.
- Assess issues of donor sustainability, include both private donors and bilateral ones

Internationalisation

- Elaborate on the scope of to a larger extent engage in other regions than Asia. What are the obstacles, challenges and possibilities?

Methodology, evaluation team and time schedule

It will be carried out by 3 persons. The team will consist of Leif Gothefors (team leader, Umeå University), Lars Åke Persson (Uppsala Univeristy) and Marita Troye-Blomberg (Stockholm University). The consultants should visit Sida/SAREC for an introduction, followed by a one-week visit to IVI where meetings with relevant staff at IVI will be held. A purposeful sample of country partners (e.g. Vietnam and India) should be selected and visited for interviews concerning their experience of partnership, capacity building, technical assistance and research activity with the IVI. The consultants should read previous reports, evaluation and memorandum from Sida and review other relevant documents. Given the broad geographic coverage of IVI and the need to consult country partners, it is anticipated that the evaluation will require 12 weeks to complete. A final timetable has yet to be determined. However, it is expected that the evaluation team will begin work in September, 2006 and submit a draft in November, 2006. A final report will be prepared within two weeks of the debriefing of interested parties.

The consultants will make their own travel arrangements. The visits will be facilitated through contacts from SAREC and IVI.

Reporting

The report should be written in English and the format and outline of the report shall follow the guidelines in Sida evaluation report – a standardised Format (see annex)

The evaluation report will include the following:

- Based on what is found regarding the above mentioned points, give concrete and realistic recommendations for improvements
- Conceptual and practical lessons learned in the process of commencing operations at IVI
- Recommendations for the strategic direction of the IVI

Annex 2, Program for visits to IVI, Seoul, National Institute for Cholera and Enteric Diseases, Kolkata, and National Institute for Hygiene and Epidemiology, Hanoi

Visit to IVI, Seoul

Thursday October 12:

Welcome

Review of Terms of Reference and proposed Agenda
Video presentation
Tour of Facilities

Friday October 13

Institutional overview

Overview of background, governance, evolution, niche and
Strategic vision – JC
Overview of institute financial status – MG
Overview of resource mobilization (local and international) vis-à-vis donor sustainability – LJ
Overview of relationship with Seoul National University, other Korean universities, and institutions outside Korea – JC
Overview of translational research – LJ
Overview of laboratory research – CC
Overview on how IVI is contributing to the UN Millennium Development Goals and Global public goods – JC

Working lunch and Discussion

Cholera

Review of DOMI – JC
Cholera Vaccine Initiative (CHOVI) – LJ
Vaccine development and technology transfer – RC
Clinical studies of new WC vaccine
Assay development – SH
Genomic studies – Jongsik
Discussions with review team

Saturday October 14

Shigella

Review of DOMI – JC
Vaccine development –RC
Molecular studies – Dongwook
Animal models – Mina Kweon

Working Lunch and Discussion

Typhoid

Review of DOMI and Parachina – Leon Ochiai (LO)/Xuanyi Wang (XW)
Investment cases and plans for new Vi introduction activities – LJ
Vi technology transfer – RC

Assay development – RC and SH
Conjugate vaccine development and plans – Clark and RC
Genomic studies – Dongwook

Japanese encephalitis
Review of translational programs – XZ
Plans – LJ

Pediatric dengue vaccine initiative (PDVI)
Review of program and plans – HM

Rota virus
Review of program and plans – PK

Encapsulated respiratory bacteria
Review of program and plans – PK

Discussion

Sunday October 15
Rest day

Monday October 16
Crosscutting activities
Vaccine safety – JC
Mucosal vaccine delivery systems – CC
Dendritic cell as vaccine processors – Mina Kweon

Plans for North Korea – JC
BSL 3 plus and A 3 facilities – CC
Training and capacity building – LJ /RC

Working lunch and Discussion

Small groups meetings
Meeting at Ministry of Foreign Affairs, Dr Kyung-Wha Kang
Dinner with staff at IVI

Tuesday October 17
Small groups meetings

Lunch
Wrap up and debriefing by review team

Visit to National Institute for Cholera and Enteric Diseases, Kolkata

Agenda for Sida team February 6 to 8, 2007

February 6
Pick up from airport, transfer to hotel

February 7
10 am: Pick up from hotel
10:15: Meet with Drs Sur and Manna

Presentation of IVI projects in NICED
Set-up of IVI-NICED collaboration
Typhoid
Cholera
Socio-behavioural studies
Economic studies
1 pm: Lunch
2–5:30 pm: Continuation of discussion
Tour of facilities (Data room, Laboratory, JICA building)

February 8
10 am: Pick up from hotel
10:15 am: ID Hospital outpost, Field site visit
1 pm: Lunch
2 pm: Discussion with Drs Bhattacharya and Sur

February 9
7 am: Pick up from hotel
Depart Kolkata

Visit to National Institute for Hygiene and Epidemiology, Hanoi

Sida team February 8–11, 2007

February 8
Arrival

February 9
9–11 am Discussion with Dr Dang Duc Anh, Vice Director of NIHE, and Dr Doan Thi Thuy, Deputy General Director of Vabiotech, and tour of the vaccine production facilities.

NIHE staff was not available for any further discussions and cancelled the rest of the planned program.

Februay 10–11
In Hanoi

Annex 3, List of contacts

The following persons have participated in discussions, been interviewed or otherwise been involved in the collection of data and information for the evaluation mission.

IVI, Seoul	Dr John Clemens	Director General	
	Dr Luis Jodar	Director General for Research Coordination, Programs and Institutional Development	ljodar@ivi.int
	Michael Goon	Deputy Director General for Administration and Finance	mgoon@ivi.int
	Dr Cecil Czerkinsky	Deputy Director General for Laboratory Sciences	cczerkinsky@ivi.int
	Dr Paul Kilgore	Senior Scientist (Epidemiology)	pkilgore@ivi.int
	Ok Ju Hwang	Government Relations Liaison	ojhwang@ivi.int
	Dr Harold S. Margolis	Director Pediatric Dengue Vaccine Initiative	hsmargolis@pdvi.org
Ministry of Foreign Affairs and Trade (MOFAT)	Dr Kang Kyung-wha	Director General for International Organizations, MOFAT	khkang98@mofat.go.kr
Bioindustry Association of Korea	Prof. Wan Kyoo Cho	President Bioindustry Association of Korea	wkchoh@yahoo.co.kr
National Institute of Cholera and Enteric Diseases, Kolkata, India	Dr S.K. Bhattacharya	Additional Director-General	bsujit@vsnl.net
	Dr Byomkesh Manna	Assistant Director	Mannab2000@yahoo.co.in
	Dr D Sur	Deputy Director	
National Institute of Hygiene and Epidemiology, Hanoi, Vietnam	Dr Dang Auc Anh	Vice Director, NIHE	ducanhnihe@hn.vnn.vn
	Dr Doan Thi Thuy	Deputy General Director, Company for Vaccine and Biological Production No 1	doanthuy@vabiotechvn.com
ICDDR,B, Dhaka, Bangladesh	Dr David Sack	Executive Director ICDDR,B	dsack@icddrb.org
The Swedish Institute for Infectious Disease Control (SMI), Stockholm, Sweden	Dr Ragnar Norrby	Director General	ragnar.norrby@smi.ki.se
Göteborgs universitet, Gothenburg, Sweden	Dr Jan Holmgren	Professor Dept of Microbiology and Immunology, Gothenburg University	jan.holmgren@microbio.gu.se
National Public Health Institute, Helsinki, Finland	Dr Hanna Nohynek	Professor	Hanna.nohynek@ktl.fi
Sanofi Pasteur MSD, Lyon	Dr Luc Hessel	Executive Director, Medical and Public Affairs	lhessel@spmsd.com
Asia Pacific GSK, Singapore	Dr Hans L Bock	Director, Clinical R&D and Medical Affairs	Hans.l.bock@gsk.com
Fogarty International Center, N.Y., USA	Dr Roger I. Glass	Director	glassr@mail.nih.gov
GAVI	Dr Bo Stenson	Member, GAVI Fund Affiliate Board of Directors	
WHO	Dr Marie-Paule Kieny	WHO's Initiative of Vaccine Research	kienym@who.int

Annex 4, Schedule for vaccinology training course

The 6th International Advanced Course on Vaccinology in Asia-Pacific Regions IVI, Seoul, May 15–20, 2006

Agenda

Day 1: Monday, May 15, 2006

0900	0930	Welcome address and IVI introduction	J Clemens/L Jodar
Epidemiology			
		Chairperson: P Kilgore	
0930	1030	Observational methods in vaccine evaluation	L Rodrigues
1030	1045	Coffee break	
1045	1215	Periods and measures of transmissibility	L Rodrigues
1215	1330	Lunch	
1330	1415	Advanced concepts in vaccine evaluation	L Rodrigues
1415	1500	Molecular typing of pathogen: principles and methods	JS Chun
1500	1515	Coffee break	
Immunobiology			
		Chairperson: L Rodrigues	
1515	1615	Vaccine concepts: immune responsiveness to vaccines (productive versus suppressive immunity)	C Czerkinsky
1615	1715	Basic principle of immune responses: innate versus adaptive immunity	H Tang
1800	2000	**Welcome reception**	at the IVI Lobby

Day 2: Tuesday, May 16, 2006

Moving from discovery to licensed product (I)			
		Chairperson: H Tang	
0830	0915	Antigen delivery systems (adjuvant, DNA-based vaccines, recombinant viral vaccines)	M Friede
0915	1000	Immunological basis of mucosal vaccines	C Czerkinsky
1000	1015	Coffee break	
1015	1100	Vaccine delivery systems (nasal, oral, aerosol, dermal, jet injector delivery)	M Friede
1100	1145	Development and GMP production of vaccines: shigella ribosomal vaccines	R Carbis
1145	1230	Lunch	
		Chairperson: M Friede	
1230	1430	New vaccine evaluation: phase I–III	P Kilgore
1430	1445	Coffee break	
1445	1545	Phase I–III rotavirus vaccines clinical trials: case study	D Steele
1600		Seoul sightseeing	

Day 3: Wednesday, May 17, 2006

Moving from licensing to introduction

		Chairperson: N Dellepiane	
0900	0940	The changing regulatory environment: the rotavirus vaccine case	I Gust
0940	1010	Asian regulatory perspective and trends	S Cook
1010	1040	Regulatory pathways and procedure for acceptability of vaccines for purchase by UN agencies	N Dellepiane
1040	1120	AEFIs and risk communication	F Andre
1120	1135	Coffee break	
1135	1300	Round table discussion:	Chaired by I Gust
		The science, practice, public opinion – a pragmatic approach?	Participants: S Cook, F Andre, N Dellepiane, L Jodar
1300	1400	Lunch	

Product development partnerships

		Chairperson: I Gust	
1400	1600	PPPs: 3 models of accelerating the development and introduction of developing country vaccines with local producers/big pharma:	
		Group A meningococcal vaccines (40 mins)	L Jodar
		Malaria vaccines (40 mins)	K Amfo
		HPV vaccines (40 mins)	V Tsu
1600	1615	Coffee break	
1615	1635	Technology transfer	R Carbis
1635	1730	Round table discussion:	Chaired by: I Gust R Carbis, K Amfo, L Jodar, H Margolis, V Tsu, R Mahoney
1730	1800	IVI laboratory tour	R Carbis

Day 4: Thursday, May 18, 2006

Moving from licensing to introduction (2)

		Chairperson: H Margolis	
0900	1000	Phase 3B studies: demonstration projects	J Clemens
1000	1030	Typhoid demonstration trials in Asia: case studies	L Ochiai
1030	1045	Coffee break	
1045	1115	Herd immunity conferred by killed oral cholera vaccines in	
		Bangladesh: a re-analysis	J Clemens
1115	1200	Round table discussion:	J Clemens, L Ochiai, H Margolis
1200	1300	Lunch	

Product development partnerships (2)

		Chairperson: J Clemens	
1300	1320	The Pediatric Dengue Vaccine Initiative: clinical evaluation and R&D	H Margolis
1320	1340	The PDVI: partnerships and access	R Mahoney
1340	1440	Break-up group discussions	
1440	1455	Coffee break	

1455	1555	Group discussion	I Gust, J Clemens, H Margolis, R Mahoney
1555	1655	Presentations from groups	

Day 5: Friday, May 19, 2006

Moving from licensure to use (3)

		Chairperson: P Namgyal	
0830	0915	Health economics: principles and methods	D Walker
0915	1000	Socio-behavioural aspects of vaccine evaluation	A Pach
1000	1045	Development of investment cases for accelerated introduction of typhoid vaccines in selected countries in Asia	
		Case study: Vietnam	L Jodar
1045	1100	Coffee break	
1100	1230	Introduction of new vaccines in the Asia-Pacific region:	
		Challenges and opportunities	P Namgyal
		Rotavirus vaccine introduction	T Nelson
		Discussion on participant's practical experiences	
1230	1330	Lunch	

Programmatic Considerations:

1330	1400	Financing mechanisms: the different models/options/GAVI	P Lydon
1400	1500	Round table discussion	Chaired by P Lydon I Gust, F Andre, P Namgyal, L Jodar, D Walker
1500	1515	Coffee break	
		Chairperson: F Andre	
1515	1630	Sharing experience: injection safety assessment and adverse event monitoring	A Amarasinghe
		Discussion on participants' practical experiences	
1630	1645	Coffee break	
1645	1800	Sharing experience: vaccine introduction in GAVI Programs – cold chain, logistics	D Kohl
		Discussion on participants' practical experiences	

Day 6: Saturday, May 20, 2006

Special lectures

		Chairperson: L Jodar	
0900	1030	Keynote closing speech – the future of vaccines and vaccination with special emphasis on avian flu and other pandemics	I Gust
1030	1100	Coffee break	
1100	1200	Closing ceremony	J Clemens/L Jodar
1200	1400	Lunch	

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Department for Africa

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sida@sida.se

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Phone: +46 (0) 8 698 51 63
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Homepage: http://www.sida.se

SWEDISH INTERNATIONAL DEVELOPMENT COOPERATION AGENCY
SE-105 25 Stockholm, Sweden
Tel: +46 (0)8-698 50 00. Fax: +46 (0)8-20 88 64
E-mail: sida@sida.se. Homepage: http://www.sida.se