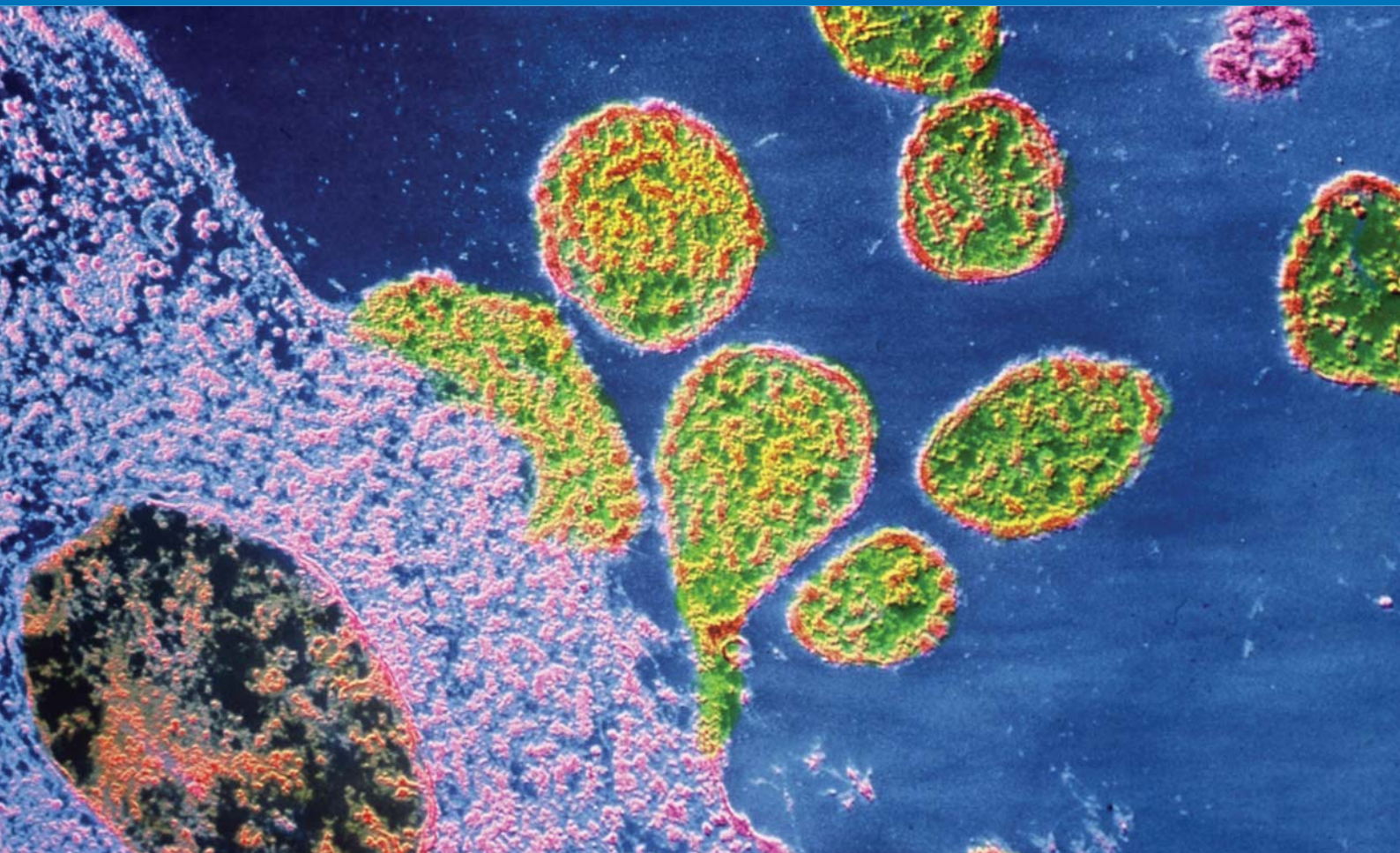
World Health Organization

The Initiative for Vaccine Research
Report 2006–2007

Department of Immunization, Vaccines and Biologicals



The Initiative for Vaccine Research

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Acronyms

AAVP	African AIDS Vaccine Programme
ADIP	Accelerated Development and Introduction
AMC	Advanced Market Commitment, new innovative financing mechanism
ARI	Acute respiratory infection
ARV	Antiretroviral
BMGF	The Bill & Melinda Gates Foundation (USA)
CDC	Centers for Disease Control and Prevention (USA)
DSMB	Data Safety Monitoring Board
DTP	Diphtheria, tetanus and pertussis
EC (DGR)	European Commission (Directorate General for Research)
ECBS	Expert Committee on Biological Standardization
EDCTP	European and Developing Countries Clinical Trials Partnership
ELISA	Enzyme-Linked ImmunoSorbent Assay
EPI+	WHO/IVB team working on immunization programmes
ETEC	Enterotoxigenic *Escherischia coli*
GADI	Global Adjuvant Development Initiative
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HVI	Joint WHO–UNAIDS HIV Vaccine Initiative
IARC	International Agency for Research on Cancer
IAVI	International AIDS Vaccine Initiative
ICH	International Conference on Harmonization
ICO	Institut Català d'Oncologia (Spain)
IND	Investigational new drug
IVB	WHO Department of Immunization, Vaccines and Biologicals
IVI	International Vaccine Institute (Republic of Korea)

IVR	WHO Initiative for Vaccine Research
LAIV	Live attenuated influenza vaccine
LSHTM	London School of Hygiene and Tropical Medicine (UK)
MCRI	Murdoch Children's Research Institute (Australia)
MVI	Malaria Vaccine Initiative at PATH
MVP	WHO-PATH Meningitis Vaccine Project
NIAID	National Institute of Allergy and Infectious Diseases (USA)
NIH	National Institutes of Health (USA)
PATH	Program for Appropriate Technology in Health
PDVI	Pediatric Dengue Vaccine Initiative at IVI (Republic of Korea)
PRNT	Plaque reduction neutralization test
QSS	WHO/IVB Quality, Safety and Standards team
R&D	Research and development
SAGE	Strategic Advisory Group of Experts on immunization
SIA	Supplemental Immunization Activity
SIDA	Swedish International Development Cooperation Agency (Sweden)
STEP	Trial study of 3000 subjects at high risk for HIV infection, designed to test the efficacy of the Merck Ad5 trivalent vaccine
TB	Tuberculosis
TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
TOC	Test of concept
TPP	Target product profile
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development (USA)
WHO	World Health Organization

1 Introduction

The Initiative for Vaccine Research – now in its eighth year – is an international team of dedicated scientists, managers and technical experts whose tasks are to facilitate the development of vaccines against infectious diseases of major public health importance, to promote the improvement of existing immunization technologies, and to make these advances available to the people who need them the most. This report describes the contribution of the Initiative during 2006–2007 towards these goals.

1.1 The global vaccine research and development landscape

Global immunization has made considerable progress during the last 10 years. Among the indicators usually employed to assess the efficiency of immunization activities, and to monitor progress towards relevant targets of the UN Millennium Development Goals, the following demonstrate this progress:

- The number of countries with DTP3 (three doses of diphtheria-tetanus-pertussis vaccine) coverage below 50% decreased from 20 countries in 2000 to only 7 countries in 2006.
- Global coverage with the third dose of hepatitis B vaccine in infants has increased from 18% in 1999 to 60% in 2006.
- The number of global measles deaths dropped by 68% between 2000 and 2006.

These are great successes. In applauding the progress of immunization activities over the last years, WHO's Director-General noted, "Increasing population coverage has reinvigorated the vaccine market. It has also stimulated R&D for new vaccines for diseases prevalent in the developing world."[1] This global progress, however, hides the fact that in some districts, in countries with high national coverage, DTP3 coverage is still below 50%, and that hepatitis B vaccine coverage in south-east Asia remains less than 30%. Special efforts are therefore needed to improve coverage in these populations.

Fortunately, the new vaccines' pipeline has considerably expanded, giving hope that many new products will become available for introduction into immunization programmes and, as a result, decrease the number of deaths from communicable diseases (Fig. 1), which will be essential to reach the objectives of the Millennium Development Goals.

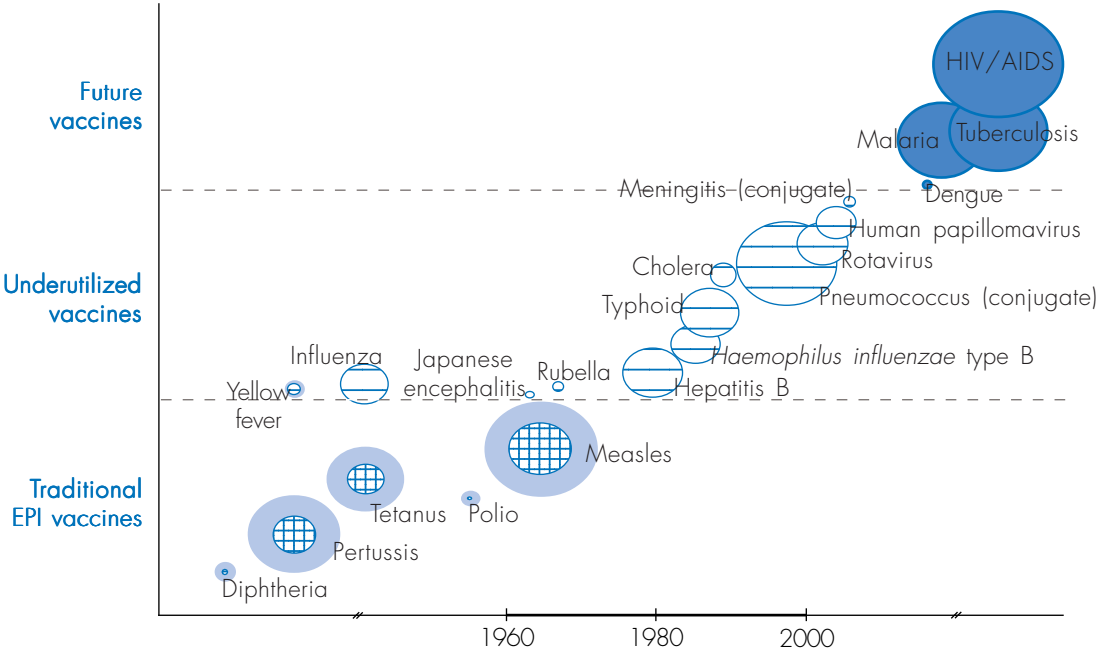
1.2 Highlights of IVR successes in 2006–2007

The following paragraphs spotlight some of the major achievements of IVR over the last two years. A more detailed account of these activities can be found in the Sections 2–4.

NEW VACCINE AGAINST MENINGITIS IN AFRICA ON THE HORIZON

Promising results from a Phase II trial of a candidate meningococcal conjugate vaccine in Mali and the Gambia, released in June 2007, pointed to the potential elimination of deadly meningococcal epidemics that have long afflicted 21 sub-Saharan African "meningitis belt" countries. This trial took place under the aegis of the Meningitis Vaccine Project, a partnership between WHO and the international, non-profit organization PATH.

FIG. 1. TIMESCALE OF VACCINE DEVELOPMENT



Area of circles is proportional to the number of deaths (2002 data). Shaded areas are proportional to the number of deaths prevented by vaccination.

Adapted from Serdobova I, Kieny MP. Assembling a Global Vaccine Development Pipeline for Infectious Diseases in the Developing World. *American Journal of Public Health*, 2006, 96(9):1554–59.

MEASLES AEROSOL VACCINE MOVING TO PROOF-OF-CONCEPT EVALUATION

Measles vaccine is highly effective and relatively inexpensive. The current route of administration through subcutaneous injection requires trained medical personnel, and carries the risk of infection from blood-borne pathogens through unsafe use and disposal of syringes and needles. Administration of measles vaccine by the respiratory route eliminates this risk. In 2007, Phase I clinical trials of a measles aerosol vaccine, carried out at three sites in India, yielded promising results in terms of safety and immune response. A pivotal trial is planned in India during the first semester of 2008.

ENHANCED INTERNATIONAL EFFORTS FOR MALARIA AND HIV VACCINES

A global strategy (the *Malaria Vaccine Technology Roadmap*) aimed at accelerating the development of effective malaria vaccines, was endorsed by major funders of malaria vaccine development. The Roadmap was officially launched at the 2006

Global Vaccine Research Forum in Bangkok. The most advanced malaria candidate vaccine (RTS,S/AS02) was shown to be able to induce 50% protection against severe disease up to 18 months after vaccination.

In the HIV vaccine field, the 2006 G8 Summit in St Petersburg reaffirmed high-level political support for the development of vaccines against the pandemic. Equally important has been the growing number of low- and middle-income countries participating in the preparation and conduct of HIV vaccine clinical trials. WHO and UNAIDS provide a forum for discussion on the development of policies, norms and standards for HIV vaccine trials, with a special focus on developing countries.

In November 2007, the First Lady of Rwanda, Mrs Jeannette Kagame, was appointed the High Representative for the African AIDS Vaccine Programme (AAVP). In this capacity, she will raise awareness among decision-makers in support of HIV vaccine R&D and for the Programme. IVR also announced at the 2007 AAVP Forum that four new centres of excellence had been established in Africa to strengthen capacity in the most needed areas of HIV vaccines work.

SIX DEVELOPING COUNTRY MANUFACTURERS COMMITTED TO PRODUCE PANDEMIC INFLUENZA VACCINES

Pandemic influenza preparedness has become a major global health security priority. In this context, IVR held a consultation in May 2006 to put together a Global Action Plan to increase supply of pandemic influenza vaccines. Six developing country manufacturers received from IVR one-year grants of US$ 2–2.7 million in 2007 to support, on a pilot scale, the production of inactivated or live attenuated seasonal and H5N1 vaccine.

Projections of how many pandemic influenza vaccine courses can be made available have sharply increased, and experts now anticipate that global production capacity will rise to several billion pandemic immunization courses per year in 2010. This is due to the use of oil-in-water adjuvants that allow the production of an effective vaccine with lower antigen content. This advance was reported in October 2007 at the first meeting of the Global Action Plan Advisory Group, an independent, international committee that advises WHO on pandemic influenza vaccine production and supply issues; and at the "Third meeting on influenza vaccines that induce broad spectrum and long-lasting immune responses" convened by IVR in December 2007.

VACCINES AGAINST BACTERIAL ENTERIC DISEASES

A number of new international initiatives were launched in 2006 and 2007 in the field of vaccines against bacterial enteric diseases, which should allow effective synergies between interested parties. Among these, the WHO cholera vaccine project was initiated in a context where the Organization currently does not recommend a cholera

vaccine stockpile of the only available 2-dose international vaccine. The project intends therefore to gather the scientific evidence needed before a future stockpile of cholera vaccine can be envisaged.

WHO SETS CRITERIA FOR SUBSIDIZED VACCINES

The Advanced Market Commitment (AMC) is a financial commitment to subsidize the future purchase, up to a pre-agreed price, of a vaccine which is not yet available, if requested by a low-income country. The pneumococcal vaccine AMC – which received US$ 1.5 billion in pledges from rich countries and foundations – was selected to pilot this new financing instrument. The aim is to accelerate the control of pneumococcal disease, which causes more than 700 000 deaths in children under the age of five. As part of the AMC process, specifications for eligible products – or target product profiles (TPP) – need to be defined in advance, and IVR was tasked to develop the TPP for pneumococcal disease, which was endorsed in November 2007 by the WHO Strategic Advisory Group of Experts on immunization (SAGE).

VACCINE CLINICAL TRIALS: MEETING THE HIGHEST ETHICAL STANDARDS

Today, there is greater awareness of the importance of enhancing scientific, technical and ethical capacity in developing countries to evaluate vaccine candidates in clinical trials. In particular, these trials need to be conducted in the vulnerable populations that should benefit the most from the trial outcomes. To this end, IVR and UNAIDS developed and published in 2007 a new document on "Ethical considerations in biomedical HIV prevention trials", which offers guidance in nearly 20 areas and supersedes the UNAIDS Ethical Guidance Document issued in the year 2000.

1.3 A streamlined WHO Initiative for Vaccine Research

The vaccine research and development landscape has evolved considerably since the launch of the Initiative in 1999. Many new players and partners are now involved in accelerating novel and underutilized vaccines through the vaccine pipeline, and many more lives are now being saved. However, as more resources have emerged, so have new threats to health, the complexity and costs of technologies, and the daunting challenge of selecting vaccines for inclusion in national immunization programmes.

IVR has evolved in line with these developments, and undertook a set of actions to assess the effectiveness of its role, comparative advantages and activity focus within the global vaccine R&D framework, in order to best serve WHO's 193 Member States, and in particular developing countries. Three of these endeavours are highlighted below.

IVR STRATEGIC PLAN 2006–2009

In 2006, IVR launched a four-year, comprehensive Strategic Plan[2] that outlines the mission and structure of the Initiative, its priority-setting process and a clear set of targets and indicators to achieve pre-defined goals. The Strategy also emphasizes

the importance given to working with collaborators, partners, networks and the community to improve synergies and attain mutually agreed results. The Strategy was developed as an integral part of the Strategic Plan 2006–2009 of the WHO Department of Immunization, Vaccines and Biologicals,[3] the Global Immunization Vision and Strategy 2006–2015,[4] and the WHO Eleventh General Programme of Work 2006–2015.[5]

IVR MISSION AND STRUCTURE

IVR is tasked to provide global vision, coordination, advocacy, guidance and support for vaccine research and development. In order to meet these objectives, as set out in its Strategic Plan, and to mirror the WHO Expected Results it has set itself for the future, IVR put in place in 2006 a three-pronged approach to support the vaccine R&D pipeline as follows:

- Management of knowledge and provision of guidance and advocacy through effective partnerships to accelerate innovation for new and improved vaccines and technologies.
- Support to research and product development for WHO priority new vaccines and technologies.
- Conduct of implementation research, and development of tools to support evidence-based recommendations, policies and strategies for optimal use of vaccines and technologies.

Three functional teams oversee these areas of work. In view of the cross-cutting nature of regulatory and ethical research, and policy development, these activities are carried out under the Knowledge Management team (HVI), where the expertise in HIV, tuberculosis and malaria have been united. IVR continues its mandate in clinical research and capacity strengthening, particularly for neglected diseases and technologies of public health importance, or where IVR can play a critical coordinating role, e.g. for novel pandemic influenza vaccines, within the Product Development team (PRD). The third Implementation team (IMR) focuses on generating the evidence base to inform decisions on vaccine research, development and introduction. This includes the elaboration of target product profiles for future vaccine introduction, disease burden assessments, and health economic studies, and responds to the increased demand for tools and technologies to support decision-makers, particularly in developing countries.

It is felt that this structure reflects better the coherence of the Initiative as a holistic research and development entity, rather than a purely disease-focused programme. It will also allow a more rational use of limited human and financial resources, while remaining true to its priority-setting process.[6] The current IVR matrix and contact details of the teams can be found in Annex 4.

INDEPENDENT EVALUATION OF IVR ROLE AND FUNCTIONS

A third undertaking to improve IVR's collaboration in the global vaccine R&D arena was an independent evaluation initiated in 2007. Close to 150 stakeholders were interviewed – either individually or through an electronic questionnaire – on their appreciation of the role, effectiveness and impact of IVR. Stakeholders included WHO staff and advisory group members, IVR constituents, researchers from developed and developing countries, industry collaborators, international vaccine initiatives and the donor community. An e-database was designed to capture the responses, which remained confidential and could not be linked to an individual or institution.

Preliminary results underlined the neutrality of IVR, and thus its important convening and coordinating role among the various stakeholders in the vaccine development pipeline, from governments to industry, from policy-makers to populations. Working under the WHO emblem also reinforced the credibility of its research agenda. IVR was also remarked for its broad range of expertise, although it was felt that focus should be on a smaller portfolio of projects, especially in the product research and development area.

On the other hand, it was considered that the Initiative should increase further its impact and range of implementation research activities, with particular focus on translating research outcomes into interventions. Involving and strengthening the capacity of developing country researchers and institutions was also perceived as a priority for future focus of IVR efforts, in complement with existing clinical research being carried out under the auspices of other partners.

A full analysis of this external evaluation, expected in early 2008, will serve to guide and, where appropriate, modify IVR's workplans in the coming years.

1.4 A culture of research at WHO

In recent years, and in the light of a growing number of sister organizations working to improve the world's health, WHO has sought to solidify its role and visibility in health research. WHO's commitment to research is enshrined in its Constitution, and articulated in three of the six core functions of the Organization, namely:

- Shaping the research agenda and stimulating the generation, translation and dissemination of valuable knowledge;
- Setting norms and standards, and promoting and monitoring their implementation;
- Articulating ethical and evidence-based policy options.

Information and knowledge, moreover, constitute one of WHO's six priority areas – identified by the Director-General as she took office in January 2007 – along with stronger health systems, health security, health development, improved organizational performance and effective partnerships.

Further to discussions at the Fifty-ninth World Health Assembly in May 2006 and 120th session of the Executive Board in January 2007, a research strategy is being developed by the WHO Secretariat. Its objective is to support the Organization's mission to improve health for all people, to better define WHO's role in international health research, and to strengthen the culture and organization of research at WHO. The strategy will be presented to the World Health Assembly in 2009.

IVR, as one of the major research-focused entities within the Organization, is a key collaborator in the elaboration of this research strategy, and works closely in this field with its constituent partner, the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

Over the last biennium, IVR has also been refining its database of research activities with a view to enhancing its capacity to monitor the various categories of research and the disease and population targets of the activities it carries out, to identify gaps and to streamline reporting. An analysis of the research projects active during 2006–2007 showed IVR's increasing normative role in knowledge management and implementation research. HIV-related activities continued to generate the greatest number of activities and resources, followed closely by diarrhoeal and enteric diseases. These statistics do not take into account the US$ 15 831 000 allocated in grants in 2007 to developing countries as a critical first step towards increasing the world's supply of pandemic influenza vaccine.

Annex 2 provides a more detailed breakdown of IVR vaccine research activities during 2006–2007.

1.5 Results-based management

Results-based management is not a new way of working in WHO. Since 2000, the Secretariat is accountable for achieving the Organization-wide Expected Results set out in the WHO Medium-term strategic plan 2008–2013 and Proposed programme budget 2008–2009.[7] The principal Organization-wide Expected Result related to vaccine R&D, to which IVR is directly aligned, is:

> "New knowledge, intervention tools and strategies that meet priority needs for the prevention and control of communicable diseases developed and validated, with scientists from developing countries increasingly taking the lead in this research."

Planning, performance monitoring and reporting of all vaccine R&D efforts across the different levels of the Organization must all relate to this global Expected Result. To ensure the relevance of this goal, each level of the Organization – headquarters, country offices and regional offices – establishes its own expected results, with indicators and targets to monitor at regular intervals the progress being made and

identify any hurdles encountered. At the global level, IVR set itself three expected results for the period 2006–2009, in the areas of: knowledge management; research and product development; and implementation research. This progress report is therefore structured around activities to reach the targets of these expected results, and a summary of progress made to date against the indicators and targets set is provided in Section 5.

1.6 IVR regional and country office colleagues

Given that the primary focus of IVR vaccine R&D efforts is in developing countries, IVR works very closely with governments and public health institutions at the national level, through its country and regional offices. In addition to the day-to-day teamwork, regional staff meet regularly with other colleagues at global forums such as meetings of SAGE and the Global Forum for Vaccine Research. These are valuable opportunities to review the landscape and discuss challenges in implementing activities. A good example of IVR collaboration with regional colleagues during 2006–2007 is the effective joint response to the impending threat of a pandemic influenza outbreak (see box).

1.7 IVR partnerships

The Director-General of WHO places a high priority on working with key players in global health with whom there is a shared vision, and where this synergy can make an impact on the health of the populations we serve. Forging partnerships within the global vaccine R&D community is intrinsic to IVR's way of working. Its independent and credible position allows it to assume a variety of different roles within these partnerships, according to global needs and its comparative advantages. Important roles of IVR are to convene and coordinate the global R&D community around priority research issues, identify and stimulate vaccine research efforts for neglected disease, and collect and collate the latest state-of-the-art knowledge on advances in vaccinology. Encouraging the participation of developing country scientists and industry, and acting as a neutral broker with commercial entities, are also among the responsibilities of the Initiative.

Highlights of IVR achievements with its major partners during 2006–2007 are provided in Section 2.6 of the report.

WORKING IN SYNERGY WITH THE WHO REGIONAL OFFICE FOR SOUTH-EAST ASIA TO STRENGTHEN CAPACITY FOR PANDEMIC INFLUENZA VACCINE PRODUCTION

Although this Region is a major vaccine producing bloc, there is not a single producer of seasonal influenza vaccine, primarily due to the lack of national policy for routine use of this vaccine. Realizing the urgent need to address the looming threat of pandemic influenza, potential vaccine producers were selected in three countries of the Region to receive WHO support for the development of influenza vaccine (see Section 2.2.2). This initiative was made possible thanks to excellent teamwork with IVR regional colleagues, who disseminated timely information and stimulated interest from potential manufacturers. This large-scale project also highlights the mutual priority of IVR and the Regional Office to strengthen local capacity to develop vaccines that will benefit both global and local communities.

1.8 Looking to the future

There will be many new opportunities for IVR in 2008–2009. In addition to bringing new vaccines such as a meningitis vaccine and an aerosolized measles vaccine closer to reality, IVR will look to translate more research results into practical tools and best practices, monitor and improve the quality of clinical trials in developing countries,

promote regulatory research into novel assays and end-points, support new networks and initiatives, e.g. in the formulation of adjuvants, and scale up its capacity to respond to health security crises such as pandemic influenza and epidemic meningitis. A summary of the goals, targets and indicators for 2008–2009 is provided in Section 5.

Yet these opportunities are not without challenges. IVR will need to increase its visibility within the global immunization and vaccine research arena if it is to attract the investment necessary to provide results. It will also need to be more selective in the research it undertakes, in line with its comparative advantages and in consultation with its partners within and outside the Organization. Finally, in line with the priorities laid down for the Organization by the Director-General, IVR will make sure that the impact of its vaccine R&D efforts to improve the health of women and the health of populations in Africa are clearly visible.

1.9 Document outline

The activities of IVR over the period 2006–2007 are presented in this report according to the type of research under which they fall, i.e. knowledge management, product R&D, or implementation research. Clearly there will be overlap in some areas – as there is in a disease-focused presentation – and an attempt has been made to point the reader to related sections of interest. An index has also been included on pages 73–75 that groups together disease- and technology-focused activities. Following the substantive presentations in Sections 2 to 4, Section 5 illustrates how far IVR has achieved the goals and targets set for 2006–2007, as well as its projected milestones for 2008–2009. A series of annexes has been provided to supplement the report, namely a summary of IVR expenditure; a breakdown of activities by type of research and disease; a list of the publications of IVR staff in the scientific literature; the structure and contact details of the Initiative; a table outlining IVR's advisory bodies; and finally a list of the major Product Development Partnerships where IVR has active collaboration.

Introduction References

1 Report by the Director-General to the WHO Executive Board at its 122nd Session, 21 January 2008 (EB122/2).

2 IVR Strategic Plan 2006–2009 (WHO/IVB/06.08). www.who.int/entity/vaccine_research/documents/Final_version.pdf.

3 http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.22_eng.pdf.

4 www.who.int/vaccines-documents/DocsPDF05/GIVS_Final_EN.pdf.

5 Engaging for health. WHO Eleventh General Programme of Work 2006–2015, Geneva, 2007. http://whqlibdoc.who.int/publications/2006/GPW_eng.pdf.

6 See IVR Strategic Plan 2006–2009, Section 3.1 for a description of the priority-setting process.

7 www.who.int/gb/e/e_amtsp.html.

2 Management of knowledge and provision of guidance to accelerate innovation for vaccines and technologies

New or improved vaccines and immunization-supporting technologies are regularly becoming available, and IVR has a responsibility to maintain state-of-the-art knowledge on their status. IVR knowledge management activities include:

- reviewing the latest scientific advances and innovations;
- portfolio and knowledge management;
- increasing global access to needed vaccines including, inter alia, facilitating technology transfer to developing countries;
- communicating vaccine research-related findings through publications, the media and the IVR Internet site;
- bringing together the global vaccine R&D community for information sharing and networking;
- encouraging partnerships to advance vaccine research, development and introduction of needed vaccines;
- facilitating consultation on and implementation of ethical and regulatory requirements for vaccine clinical trials;
- reviewing clinical trial protocols;
- maintaining a database of clinical trial sites and GMP-compliant contract manufacturers; and
- analysing intellectual property rights.

Some of the most salient activities in this area in 2006–2007 are described below.

2.1 Reviewing the latest scientific advances

2.1.1 Global Vaccine Research Forum

The vaccine industry has recently undergone a renaissance. Many new vaccines that have the potential to save millions of lives are at different stages in the R&D pipeline and may become available within the next decade. The WHO Global Vaccine Research Forum brings together, every 18 months, up to 200 top researchers, scientists, public health experts, regulators and manufacturers from all over the world. The Forum's ultimate goal is to stimulate and accelerate research, development and introduction efforts on new vaccines, especially those targeting infectious diseases of public health importance in developing countries.

The Seventh Global Vaccine Research Forum, held in Bangkok in December 2006,[1] focused on: prospects for pandemic influenza vaccines; vaccines against cervical cancer; development of vaccines against HIV, malaria and tuberculosis; innovation, intellectual property rights and new vaccine production in the South-East Asia Region; and rabies as an unrecognized health priority in Asia.

The Forum will next convene in June 2008 in Paris.

2.1.2 HIV, TB, malaria and other major infectious pathogens

IVR actively monitors scientific progress on vaccine R&D for all infectious diseases of public health importance. For example, IVR published comprehensive reviews on the state-of-the-art of vaccine development for HIV, malaria, meningococcal disease and human enteric infections in a leading scientific journal.[2] WHO position papers on vaccine R&D for several diseases were published, including on pneumococcal conjugate vaccine for childhood immunization.[3] In addition, IVR shares with its partners, and in particular donor agencies such as the European and Developing Countries Clinical Trials Partnership (EDCTP), objective information on vaccine development, including bottlenecks that hinder the process. The current situation for a number of vaccines was described in an updated WHO Fact Sheet on the Development of New Vaccines in December 2006.[4]

The progress in the global tuberculosis R&D portfolio can be consulted through the annually updated "Pipeline of new tools against TB" document.[5] Progress in the global malaria vaccine portfolio can be monitored thanks to the establishment and maintenance of the Malaria Vaccine Rainbow tables[6-7] by the IVR-facilitated Malaria Vaccine Advisory Committee. Members of the Malaria Vaccine Funders' Group[8] play a key role in providing information to update the table.

IVR, in collaboration with the WHO Department of Reproductive Health and Research, finalized and disseminated the publication "Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals".[9] This information for policy-makers and health professionals on HPV, HPV-related diseases and HPV vaccines, is designed to underpin two key WHO publications on policy and practice in countries, published in 2006.[10-11] IVR also prepared an HPV vaccine fact sheet for the same audiences, which will be published in early 2008, and is tracking research on alternative schedules for currently licensed HPV vaccines, development of second generation HPV vaccines that have more types included, and data on HPV type distribution that informs on specificity of second generation HPV vaccines.

2.1.3 Pandemic influenza vaccines

H5N1 INFLUENZA VACCINE CLINICAL TRIALS DATABASE

As part of its mandate, IVR has established and maintains an exhaustive database of clinical trials carried out across the world on the development of new and improved candidate pandemic influenza vaccines.[12] At a meeting convened by IVR in February 2007 to review progress in this area, it was noted that 16 manufacturers from 10 countries were developing prototype vaccines against H5N1 influenza virus, five of which were also involved in the development of vaccines against other novel influenza viruses. The clinical trials database was updated with over 40 trials ongoing or completed at that time.[13] The fourth meeting on the evaluation of pandemic influenza vaccines will take place in early 2008.

IDENTIFYING CORRELATES OF PROTECTION AGAINST INFLUENZA

IVR co-organized with the US Food and Drug Administration and National Institutes of Health a public workshop on correlates of protection against influenza in Bethesda, Maryland, USA in December 2007. The workshop identified gaps in knowledge and recommended a plan of action to address the unique challenges in developing and evaluating vaccines that will protect against pandemic influenza; and actions to implement a global research agenda to improve efficacy assessment of pandemic influenza vaccines.

2.2 Increasing global access to pandemic influenza vaccines

2.2.1 Global action plan to increase supply of pandemic influenza vaccines

Because of the emergence and circulation of H5N1 influenza strains and the need to prepare for a possible influenza pandemic, WHO had invited over 120 stakeholders to a consultation in May 2006 to identify and prioritize practical solutions to reduce the anticipated several billion dose gap between vaccine supply and demand. The "WHO global pandemic influenza action plan to increase vaccine supply",[14] which resulted from this consultation, outlined three approaches to achieving this goal, namely (i) developing national immunization policies to increase demand for seasonal vaccine and thereby increase production capacity through market forces; (ii) increasing influenza vaccine production capacity over and above the capacity required for seasonal influenza vaccine manufacturing; and (iii) promoting research for the development of new influenza vaccines.

IVR achievements to increase influenza vaccine production capacity are described below. See Section 2.4.4 for the work of the Global Action Plan Advisory Group, including progress towards the development of new influenza vaccines.

2.2.2 Facilitating vaccine production capacity in developing countries

Ideally, outbreak response measures should target vaccination in the countries first affected. It is clearly in the interests of all countries to be prepared for pandemic influenza, and local vaccine production capacity is therefore being established in parts of the globe which currently do not produce influenza vaccines, in order to ensure greater equity in the deployment of what will certainly be a scarce resource in the early months of a pandemic.

EVALUATING TECHNOLOGIES TO INCREASE INFLUENZA VACCINE SUPPLY

IVR carried out several activities to identify influenza vaccine production technologies that could be adopted by new producers. Working with experts in influenza vaccine manufacturing technologies, IVR developed information materials[15-16] that outline the production processes used for currently licensed vaccines, and that evaluate the cost and time needed to establish production facilities for these processes. The materials, intended as a technical resource for developing country manufacturers, point to the use of live attenuated influenza vaccines (LAIV) as an attractive approach because of their

potentially high yield and simple administration system. In order to secure consensus on the above issues, IVR organized an international consultation to discuss the potential advantages of LAIV in both seasonal and pandemic vaccines.[17] Issues related to LAIV immune potency were also reviewed at the "Third meeting on influenza vaccines that induce broad spectrum and long-lasting immune responses" in December 2007, the recommendations from which have been accepted for publication in *Vaccine*.

MAPPING INTELLECTUAL PROPERTY RIGHTS

Another arm of IVR's approach to increase influenza vaccine production capacity has been the mapping of intellectual property rights on various production processes, in order to identify areas in which new manufacturers would have freedom to operate.[18]

FACILITATING TECHNOLOGY ACQUISITION BY DEVELOPING COUNTRY MANUFACTURERS

With a view to facilitating the transfer of technology to enable more vaccine production sites in developing countries, IVR provided awards to six developing country vaccine manufacturers, either to develop pilot influenza vaccine production capacity, or to establish "fill and finish" capability for influenza vaccine provided by external sources. All projects started implementing activities in mid 2007, and their initial progress is summarized in Table 1.

INFLUENZA VACCINE PRODUCTION TECHNOLOGY "HUB" FOR TECHNOLOGY TRANSFER

Identifying industry partners capable of, and willing to transfer technology to developing country manufacturers has met with several hurdles. In addition, the number of developing countries requesting technical assistance in this domain exceeds IVR current financial and human capacity. Therefore, IVR concluded an agreement with a European public vaccine producer (Netherland Vaccine Institute) aimed at establishing an egg-based pilot influenza vaccine production process suitable for scaling up and at transferring this technology to interested developing country vaccine manufacturers. The new technology "hub" will also serve as a source of know-how and training to support the efforts of developing countries to increase local vaccine production capacity.

2.3 Knowledge and portfolio management

2.3.1 Prioritization of vaccine-preventable diseases

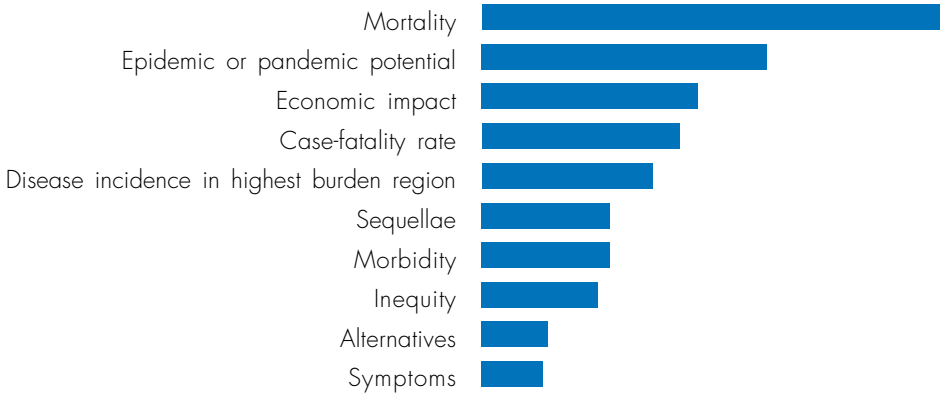
WHO has traditionally published vaccine position papers with recommendations on the appropriate use of vaccines that are licensed. However, while these papers facilitate decision-making about immunization, they do not address the growing reality that as more vaccines become available, choices need to be made on the diseases that should be tackled first. As this prioritization process is liable to influence the global vaccine market and research agenda, it is critical that WHO, as part of its normative role, helps to determine the global priorities.

TABLE 1. IVR TECHNOLOGY TRANSFER PROJECTS FOR INFLUENZA VACCINE PRODUCTION TECHNOLOGY ACQUISITION BY DEVELOPING COUNTRY MANUFACTURERS

Country/Institute	Technology objective	Progress
Brazil (Instituto Butantan)	Egg-based inactivated whole virion H5N1 with adjuvant.	A production plant and laboratories are operational and a containment laboratory is being established. Staff training has been initiated. Seed lots of H3N2 influenza vaccine have been produced, and H3N2 split inactivated vaccine prepared for animal testing.
India (Serum Institute of India)	Cell-based production of inactivated split virus.	A suitable cell system for virus growth has been identified, and the installation of a GMP-compliant pilot laboratory devoted to influenza vaccine pilot scale production initiated.
Indonesia (BioFarma)	A fill-finish facility using Japanese manufactured bulk antigens (originally for seasonal vaccine): egg-based split product.	Technicians have been trained in formulation, filling, quality control, antibody titre test and regulatory issues. Bulk vaccine was imported and equipment for quality control and production ordered. The next step will be formulating and filling the imported seasonal influenza vaccine.
Mexico (Birmex)	A blending, filling and packaging facility to perform the final production steps for Sanofi-Pasteur produced antigens: egg-based split vaccine.	Preliminary activities have been completed for the construction of a blending and filling plant for influenza vaccine production.
Thailand (Government Pharmaceutical Organisation)	Egg-based inactivated and live attenuated vaccine technology.	Key parameters for three vaccine strains have been studied for optimum high growth and haemaglutinin yield in order to select the most suitable strain for process development. Negotiations for access to the live attenuated strain are under way. Validation of the GMP pilot facility was completed.
Viet Nam (IVAC)	Egg-derived whole virion, alum adjuvanted vaccine.	Engineering and construction consultants have been selected to oversee the process of construction of a new facility. Preliminary plans for the facility have been provided to WHO.

In 2007, in collaboration with the WHO Expanded Programme for Immunization team, IVR began a project to categorize, according to public health priorities, diseases for which vaccines are either currently available but not recommended by WHO for routine use in national immunization programmes, or vaccines that should be licensed in the near future (by 2012). A landscape analysis determined that 18 vaccine-preventable diseases currently fall in these categories. A rational-consensus method was used to obtain and synthesize input from the global immunization community on the criteria they use to make public health decisions, and to compare diseases against such criteria. The initial results (Fig. 2) show the perceptions of selected participants, based on pairwise comparisons of 10 criteria and their relative importance in setting global public health priorities. While 54% of respondents chose mortality as their most important criterion, 72% considered symptoms as relatively insignificant.

FIG. 2. RANKING OF 10 CRITERIA IN TERMS OF PUBLIC HEALTH IMPORTANCE FOR DEVELOPING COUNTRIES



Using this ranking, responders classified the 18 vaccine-preventable diseases into the following three priority clusters:

Very high priority	malaria and pneumococcal disease
High priority	cervical cancer (HPV), cholera, dengue, Japanese encephalitis, meningococcal disease (ACWY), rabies, rotavirus, seasonal influenza, typhoid fever, and yellow fever
Medium priority	hepatitis A, hepatitis E, meningococcal disease (B), mumps, rubella, and varicella

These preliminary results were presented to SAGE and the GAVI Alliance Board in November 2007, and a refined version, taking account of recommendations made, will be presented in April 2008 before extending the framework to the regional priority-setting process.[19] With a view to making the categorization exercise more relevant to local settings, the extended framework may include further considerations such as vaccine characteristics.

2.3.2 Defining the target product profile for pneumococcal vaccines in the context of the advanced market commitment

The advanced market commitment (AMC) is an innovative financing instrument whereby donors agree to subsidize the purchase of a prospective vaccine up to a pre-agreed price, if it is requested by a GAVI-eligible country. Vaccine manufacturers, if they wish to receive the subsidy, need to agree in advance on a future (affordable) price for the product that they will sell to developing countries when the AMC resources have been depleted. The Secretariat to the AMC is provided by the GAVI Alliance. The goal of an AMC is to accelerate introduction of life-saving vaccine into resource-poor countries.

Eligible products need to meet minimum predefined specifications, called target product profiles (TPP). The TPP defines essential criteria that relate to the public health impact and performance of the product, covering measures of vaccine efficacy, safety, dose-scheduling, presentation and packaging. The suitability for use in GAVI-eligible countries is the overall guiding principle. Pneumococcal vaccines were selected to pilot this new financing instrument, and IVR was charged by GAVI to produce the TPP for these vaccines. During 2007, IVR conducted a series of consultations to establish a TPP that yields both substantial public health value to GAVI-eligible countries and stimulates competition among vaccine manufacturers. One major technical input was an analysis of the global distribution of pneumococcal serotypes causing invasive disease. This work – the Global Serotype Project – conducted by the PneumoADIP at Johns Hopkins University, built on strengthened disease surveillance efforts and extensive research to establish the global burden of disease caused by pneumococcal and *Haemophilus influenza* type b infections. The TPP was endorsed by the Strategic Group of Expert (SAGE) in November 2007 and communicated by the Director-General of WHO to GAVI.[20]

2.3.3 Diarrhoeal and enteric vaccines

Diarrhoeal diseases remain a leading cause of death in infants and young children and a high priority of IVR. The portfolio of pathogens and diarrhoeal and enteric diseases includes rotaviruses, enterotoxigenic *Escherichia coli* (ETEC), cholera, shigellosis and typhoid fever. During 2006–2007, IVR contributed to significant developments related to three of these diseases, with the following outcomes:

- A TPP for ETEC vaccines,[21] which contributed to the establishment of an Enteric Vaccine Initiative by the Bill & Melinda Gates Foundation and informed the

research directions of a new WHO Collaborating Centre on ETEC diagnostics and immune responses for vaccine trials in Göteborg, Sweden. An article was also published in the *Weekly Epidemiological Record* on a review of progress made in ETEC vaccine development. The review evaluated the epidemiology and successes or failures of vaccine trials in young children in developing countries and updated the previous recommendations for the field.[22]

- A unified Laboratory Manual for Rotavirus Detection and Characterization, which is now available to all regional rotavirus surveillance sites and to other interested researchers. IVR also contributed to the updated WHO position paper on rotavirus vaccines, published in the *Weekly Epidemiological Record* in 2007.[23]
- A comprehensive document on typhoid fever and vaccines against the disease, which was reviewed by SAGE in November 2007. The document described the high prevalence of typhoid fever found in recent disease surveillance in several Asian sites, its high economic burden, the significant increase and spread of antibiotic resistance and the population demand for typhoid vaccines. In view of the evidence presented, and data showing the cost-effectiveness of the new-generation vaccines, SAGE endorsed enhanced use of vaccine in regions where the disease is highly endemic, and recommended a revision of the WHO position paper on typhoid vaccine.[24]

2.3.4 Systematic review of data on aerosolized measles vaccine

In order to acquire more robust evidence and to corroborate results published prior to 2001, IVR sponsored a systematic review to examine the immunogenicity and safety of aerosolized measles vaccine one month or more after vaccination.[25] The review showed that in children of 10–36 months, seroconversion rates were similar among those vaccinated subcutaneously or by the aerosol route. Moreover, in 5–15 year olds, aerosolized vaccine was more immunogenic than the subcutaneous route. Reported side effects in the trials reviewed were mild. The review concluded that aerosolized measles vaccine appeared to be at least as immunogenic as subcutaneous vaccine in children aged 10 months and older, and thus provided strong evidence for continued IVR focus on aerosolized measles vaccine.

2.3.5 Meningococcal carriage studies in Africa

In 2007, IVR contributed to the initiation of a large multi-centre meningococcal carriage study in sub-Saharan Africa across the meningitis belt, under the leadership of the London School of Hygiene and Tropical Medicine (LSHTM). The objective of the study is to measure the effect of vaccine on carriage and transmission in 10 potential sites.[26] Progress has included the recruitment of an epidemiologist and a microbiologist at the LSHTM to formulate the full project proposal and actively work on the selection of sites across the meningitis belt. Following a meeting of all partners of the African Meningococcal Carriage Consortium held in November 2007, a comprehensive, five-

year grant proposal was finalized and submitted to the Wellcome Trust in the UK, sponsor of the initial grant.

IVR was also awarded funds for a research proposal entitled "Impact of a new and affordable conjugate meningococcal vaccine on carriage of serogroup A *Neisseria meningitidis* and disease transmission", for a pilot study to be conducted in Burkina Faso before, during, and after vaccine introduction. This is a multi-partner project between IVR, PATH, CDC, the Ministry of Health and national laboratories of Burkina Faso, and the National Institute of Public Health and Centre for Global Infections at the University of Oslo in Norway. With funding from the Research Council of Norway through the Global Health and Vaccination Research Programme, WHO and partners will start carriage studies in early 2008 in Burkina Faso, one of the first countries targeted for widespread Group A conjugate vaccine introduction. The research will be conducted as part of the African Meningococcal Carriage Consortium and the pilot study will serve to adjust research design and methods in other settings.

Finally, IVR facilitated the collection of unpublished information on meningitis in Africa and on meningococcal vaccines, and sponsored the publication of a review of the evidence in a dedicated supplement in the journal *Vaccine*.[27]

2.3.6 A new adjuvant initiative

Research and development into new vaccines against diseases such as malaria, HIV and TB does not systematically use appropriate adjuvants or formulations. This is particularly true in the public or small biotechnology sector where most immunogenicity studies rely on aluminium salts – which only induce minimal cell mediated immunity – or squalene-based water-in-oil emulsions such as ISA720, which are frequently too reactogenic for use in prophylactic vaccines and present a number of manufacturing issues. Certain proprietary adjuvants are available from private sector developers, although access is complicated by licence terms and lack of knowledge on which ones are suitable, given that direct comparisons are not readily achievable. In addition, the inability to optimally formulate vaccines has resulted in delays or failures in vaccine development.

To improve the availability of potent adjuvants, and particularly know-how on their use in order to streamline the development of new vaccines, IVR has prepared the groundwork for the establishment of the Global Adjuvant Development Initiative (GADI). The Initiative will comprise two research centres, based in Switzerland and in India, that will assume responsibility for a vast range of activities, from securing access to new molecules to sponsoring clinical trials of lead vaccine formulations. GADI will:

- undertake the evaluation, optimization and development of adjuvants using standardized readouts;
- generate new scientific knowledge and innovation on adjuvants and formulations;

- create public sector expertise on vaccine formulation and disseminate this knowledge; and
- provide vaccine formulation services in the public sector.

IVR has already performed a detailed intellectual property rights analysis and identified a range of immunostimulants and delivery systems known to work in preclinical models for which intellectual property issues may not pose a significant hurdle.

IVR has also initiated the establishment of a network of adjuvant users – called AdjuNet. Members of AdjuNet will be able to select candidate adjuvants from the GADI portfolio for GMP production, and to evaluate them in their own vaccine clinical trials. A database of all preclinical toxicology studies undertaken with adjuvants by AdjuNet members is also foreseen, as well as a web-based resource providing the latest information on adjuvants, a database of clinical trials involving adjuvants, and a forum on formulation issues.

To support the identification, evaluation and development of adjuvant candidates, IVR has established a collaborative arrangement with the US Infectious Diseases Research Institute. This collaboration will enhance the activities of GADI and AdjuNet for the harmonized screening of adjuvant development.

2.3.7 Intellectual property rights issues

It is essential for groups developing new vaccines, or generic versions of existing vaccines, to consider the intellectual property related to the technology. Many of these groups lack the technical expertise to undertake patent mapping exercises, to determine in which countries the patents have been granted, or to evaluate how far their proposed technology may infringe on existing patents.

In 2006–2007, IVR carried out a patent mapping exercise for HPV vaccines to determine the feasibility for developing country vaccine manufacturers to make generic versions of this vaccine. Similarly, a mapping exercise (see Section 2.2.2) was performed on influenza vaccine production technologies to identify which of those suitable for manufacturing vaccines against pandemic influenza were subject to granted patents. Moreover, IVR provided technical advice to Member States querying the scope and validity of patent applications relating to strains of novel influenza virus, and collaborated with the World Intellectual Property Organization on the drafting of technical documents related to the patenting of influenza virus genetic material.

2.3.8 Community education and media training

The conduct of vaccine trials, particularly in developing countries, could be seriously jeopardized by the lack of appropriate involvement and support from political leaders, communities and the mass media. With respect to HIV, these activities should constitute an important part of National HIV Vaccine Plans. In 2006–2007, at the request of

Member States, IVR supported the organization of media training workshops for Portuguese- and Russian-speaking countries, particularly since this type of training has previously focused on English- and French-speaking countries. In November 2006, a media training workshop was organized in Lisbon for African Portuguese-speaking countries in collaboration with IAVI and the WHO Regional Office for Africa, with the participation of facilitators from Brazil. The participants represented all Portuguese-speaking countries in Africa that are actively involved in broad media coverage of HIV issues and vaccine trials.

The second media training was organized in August 2007 for Russian-speaking countries, following a request from the Russian Duma [Parliament] to address reported misinformation and inadequate coverage of immunization programmes and clinical trials in the Russian media. The workshop was attended by leading Russian-speaking journalists from the Baltic countries, Belarus, Georgia, Russia, Ukraine and Uzbekistan, who received extensive information on vaccine development and clinical trials, ethical considerations and the importance of community involvement.

2.4 Activities related to IVR advisory committees

An important part of IVR's work is to convene the leading experts in generic and topical vaccine research and development in order to gather the best evidence and to reach consensus on complex scientific or technical issues. An external review of the advisory groups of the Department of Immunization, Vaccines and Biologicals was conducted by an independent group of experts and endorsed by SAGE in 2007. Following the recommendations of SAGE, IVR streamlined the number and type of its advisory bodies with a view to ensuring advice on strategy, priorities and gaps in vaccine R&D from the best available expertise and knowledge. New committees were established on Quantitative Implementation Research and on Pandemic Influenza, the latter in collaboration with the Global Influenza Programme. In addition, an updated selection process for membership of IVR advisory bodies was initiated to improve the transparency and efficiency of their operations.

All committees advise on the respective IVR work plan and make recommendations on scientists and institutions suitable to carry out R&D projects in line with the public health relevance of IVR objectives. A list of IVR's advisory committees can be found in Annex 5. The following paragraphs summarize the focus of IVR advisory bodies during 2006–2007.

2.4.1 IVR Vaccine Advisory Committee

The functions of the IVR Vaccine Advisory Committee (IVAC) are to provide strategic advice, help strengthen interaction among major stakeholders in the field of vaccine R&D and optimize synergies. At its meeting in April 2007, IVAC discussed IVR's position within global vaccine R&D efforts, as well as within WHO's overall research strategy 2006–2009, particularly related to the role of research among the six core

functions of the Organization. Members joined WHO's concern that sufficient vaccine may not be available in the event of an influenza pandemic and applauded IVR's efforts to address this issue. Given the potential impact of adjuvants on producing new vaccines, IVAC also supported the new Global Adjuvant Development Initiative as a priority for IVR.

In recommending a stronger focus on implementation and facilitation research, IVAC members made suggestions for increased focus within the IVR work plan, such as capacity building, advice on vaccine introduction, product development for orphan vaccines and technologies, and acting as a global focal point for independent identification of research gaps and operational research to support decision-making.

In summary, while welcoming IVR's special relations with industry and the private sector for product development, IVAC emphasized the importance of the neutrality, competence and independence of IVR, both at the financial and decision-making levels.

2.4.2 WHO–UNAIDS HIV Vaccine Advisory Committee

The WHO–UNAIDS HIV Vaccine Advisory Committee (VAC) reports to IVR and is composed of the world's experts in HIV vaccine development, clinical trial design, regulatory and ethical aspects, as well as community representatives. The work accomplished by this highly active forum goes well beyond attendance at annual conferences. During 2006–2007, VAC reviewed four clinical trial protocols to test the leading candidate HIV vaccines. Members recommended that critical attention be given to safety issues, ethical standards and the potential regulatory implications that may arise during the conduct of these trials.

VAC also conducted in June 2006 an external review of a large HIV vaccine efficacy trial in Thailand, at the request of the Ministry of Health. The recommendations from the review helped the principal investigators to adjust the ethical standards of the trial and further improve community involvement and participation in this trial of 16 000 volunteers.

To facilitate national decision-making on sensitive issues in relation to conduct of HIV vaccine trials at the highest scientific and ethical standards, IVR, under the auspices of VAC, developed and published policy and position papers on issues related to the involvement of women and adolescents in HIV vaccine trials,[28] novel approaches to vaccine efficacy trial design (Phase IIB test-of-concept trials)[29] and access to care and treatment.[30] These papers were produced in collaboration with partners and representatives from developing country governments and communities.

2.4.3 Malaria Vaccine Advisory Committee

The IVR Malaria Vaccine Advisory Committee (MALVAC) provides guidance and oversight on activities related to malaria immunization. The primary focus of the Committee is on spearheading activities that enhance and strengthen understanding of

the science and knowledge of evaluation of malaria candidate vaccines. In 2006–2007, the Committee reviewed the landscape and progress in malaria vaccine development to identify neglected areas of research, such as vaccine development against *Plasmodium vivax*, and malaria in pregnancy, which were the focus of technical consultations held during MALVAC meetings. The committee was also a key contributor to the launch of the *Malaria Vaccine Technology Roadmap* in December 2006.

2.4.4 Global Action Plan for Pandemic Influenza Vaccines Advisory Group

In follow-up to the "Global pandemic influenza action plan to increase vaccine supply" (see Section 2.2.2), the Global Action Plan Advisory Group first met in October 2007. The independent committee of 10 international members reviewed progress in the clinical development of novel H5N1 vaccines and considered promising technologies for pandemic influenza vaccines, including that for live attenuated influenza vaccines (LAIV).

The Global Action Plan Advisory Group also endorsed a new business plan developed by McKinsey Consultants for IVR which recommends, in parallel to the promotion of seasonal influenza vaccine programmes, two further options to increase vaccine production capacity, namely:

- supporting industry to sustain the production capacity expected to be available by 2010 beyond seasonal demand; and
- adapting selected new vaccine production facilities to convert, at the onset of a pandemic, from producing inactivated vaccine to live attenuated vaccines.

This latter option could, by 2012, bridge the expected supply–demand gap.

2.4.5 Advisory Committee for Diarrhoeal and Enteric Disease Vaccines

The Advisory Committee for Diarrhoeal and Enteric Disease Vaccines meets annually to evaluate new developments in the field, identify gaps in knowledge, prioritize activities where IVR should provide leadership, and to review budgets and research proposals submitted to IVR for funding. The Committee met in Cairo in 2006 and in Lisbon in 2007 in conjunction with the Fourth International Conference on Vaccines Against Enteric Diseases. Members made recommendations on the diagnostic and immune assays required for further research on ETEC in the field; on vaccines currently under development; and on the scientific meetings being organized by IVR to develop recommendations or strategies for diarrhoeal and enteric vaccines.

2.4.6 Advisory Committee on Dengue and other Flavivirus Vaccines

The advisory committee on flavivirus vaccines provides overall guidance to WHO and its partners on the development and evaluation of new dengue and Japanese encephalitis vaccines. It also provides technical advice in relation to the yellow fever vaccine. The Committee met in Geneva in 2006,[31] and in Ho Chi Minh City in 2007.

A separate session of these meetings is dedicated to discussions with the private sector to review the latest information on the evaluation of dengue vaccines.[32] Over the past two years, the Committee has overseen the production of several guidance documents on this aspect (see also Section 3.2.4). An article was also published in 2006 updating the WHO position paper on Japanese encephalitis vaccines.[33]

2.4.7 Human Papillomavirus Vaccines Expert Advisory Committee

The third meeting of the Human Papillomavirus Expert Advisory Committee was convened by IVR in September 2007. The Committee is finalizing a Background Paper that will serve as the scientific basis for future WHO recommendations regarding HPV vaccine, scheduled for discussion at SAGE in 2008. The advisory body also defined high priority research studies, including clinical trials, which IVR has since been promoting among researchers and industry. IVR also contributed to the expansion of the HPV Laboratory Network, created to set and apply international standards for HPV serology and antibody assays in the assessment of vaccine quality and impact; and to establish vaccine manufacturing standards and quality. This activity resulted in the publication in the WHO Technical Report Series of "Guidelines to assure the quality, safety and efficacy of recombinant Human Papillomavirus virus-like particle vaccines."[34]

2.4.8 Quantitative Immunization and Vaccines Research Advisory Committee

Following a recommendation by SAGE in 2006, the Quantitative Immunization and Vaccines Research Advisory Committee (QUIVER) was established to advise the IVR Secretariat on quantitative research issues, particularly those related to estimating the burden of vaccine-preventable diseases, health economics and modelling vaccine interventions. At its first meeting in September 2007, the Committee advised on the estimation of the burden of measles and tetanus; the modelling of vaccine interventions for measles and for pandemic influenza; economic evaluations of vaccines; as well as on other analytical components of operational and implementation research.

2.5 Collaboration with partnerships

IVR seeks to work with partners from a wide variety of disciplines to ensure that promising vaccine candidates advance through the R&D pipeline and reach those who need them. These partners include governments – essentially in developing countries – policy-makers, clinical researchers, monitoring and evaluation specialists, networks for developing country clinical trials, implementation partners, ethicists and regulatory experts, international agencies, community programmes, manufacturers and donor agencies.

2.5.1 The African AIDS Vaccine Programme

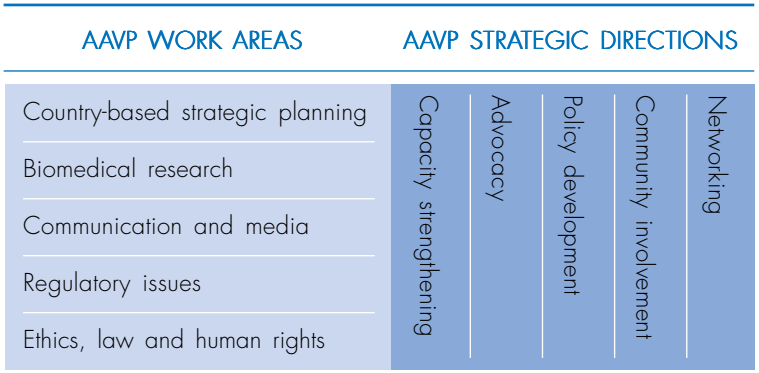
Since its inception in 2000, the African AIDS Vaccine Programme (AAVP) has become a reputed and active voice for the development of a safe, effective and affordable HIV vaccine suitable for use in Africa. The international HIV vaccine landscape has also significantly changed, with increased political commitment and partnerships, such as the Global HIV Vaccine Enterprise, to accelerate the development of HIV vaccines.

During 2006–2007, the AAVP continued its focus on advocacy, policy and capacity strengthening with a view to ensuring the highest scientific, ethical, regulatory and legal standards for HIV vaccine trials. Currently, eight African countries are working within the framework of National AIDS Vaccine Plans, and the guidelines to assist countries in the development of their National Plans have been updated.

To monitor the role and function of the AAVP in the evolving global environment, IVR commissioned an external evaluation of the AAVP. Advocacy and coordination in support of HIV vaccine development for Africa were listed as top priorities for the AAVP by the review team. In line with this finding, IVR developed an advocacy strategy designed to serve the collective interests of all AAVP partners, and intended to be used in a consistent, mutually reinforcing way.

Following an extensive consultation with all international partners, a new Five-Year Strategic Plan was launched in 2006 covering the period 2007–2011.[35] As part of this Strategic Plan, a refined organizational structure was put in place to ensure the autonomous implementation of AAVP priorities by African institutions and experts under five work areas, which in turn support five strategic directions (Fig. 3). Activities will be implemented by four AAVP Centres of Excellence in complement with the strategic support provided by IVR. In 2007, IVR facilitated the selection of three Centres of Excellence through an open call for candidate institutions in Biomedical research; Ethics, law and human rights; and in Communication and media. The search for a Centre of Excellence to take responsibility for regulatory issues is in progress. IVR will continue to provide core financial and technical support for a certain period, at the end of which each Centre of Excellence is expected to have become financially self-sufficient.

FIG. 3. A FRAMEWORK OF THE 5-YEAR AAVP STRATEGIC PLAN (2007–2011)



As in the past, all AAVP activities within the new framework will be implemented based on an extensive analysis of gaps and needs, and in close collaboration with partners conducting HIV vaccine work in Africa. Immediate challenges will be for AAVP to harmonize its activities with other programmes being implemented in Africa, such as laboratory networks in support of access to antiretroviral treatment, and capacity building activities for either biomedical prevention trials, such as microbicides, or other vaccine trials, such as malaria.

A major event in November 2007 was the 4th AAVP Forum which took place in Abuja, Nigeria. The Forum was attended by some 140 participants from 12 African countries, including scientists, research agencies, and regional and international institutions involved in HIV vaccine R&D. The theme of the Forum was to "build bridges between HIV vaccines and other preventive research for the effective use of resources in Africa". Thematic working groups made recommendations on the four work areas of the AAVP, and the Forum approved the new AAVP Strategic Plan.

Highlights included the announcement of Mrs Jeannette Kagame, First Lady of Rwanda, as the AAVP High Representative. As an outstanding political champion for the AAVP, Mrs Kagame agreed to help the Programme reach a wider audience to inform, educate and advocate in favour of an AIDS vaccine for Africa. Clear financial commitments were made by African governments for the Programme, with the Abuja Statement calling for Heads of State of other African nations to follow suit. At the AAVP Steering Committee meeting that followed the Forum, members discussed preparations for the AAVP to become a fully independent African organization by 2010, based in an African country. To ensure this transition happens smoothly, it was agreed to initiate a process of consultations to develop a business plan with funding needs, and to present the new structure at the next AAVP Forum in Kampala, Uganda in 2009.

For more information, visit www.who.int/vaccine_research/diseases/hiv/aavp/en/.

2.5.2 The Global HIV Vaccine Enterprise

In March 2007, IVR convened a consultation to discuss strategies for communication of HIV vaccine efficacy trial results, in particular trials of T-cell targeted candidate vaccines aiming to control virus replication and thus prevent the development of disease. The consultation was organized jointly by WHO and the Global HIV Vaccine Enterprise in anticipation of interim results from the two large-scale Phase IIB TOC (test-of-concept) trials with prime-boost combinations. It was agreed that, prior to the release of data from the efficacy trials, two international groups – a WHO/Enterprise Coordinating Group and a Communications Group – should be convened to advise on specific activities to address current gaps. For example, recognizing WHO's role and expertise in the area of vaccine regulation and clinical trials, IVR was requested to convene an expert group on the "Definition of HIV vaccine efficacy based on surrogate markers", the outcome of which is discussed under Section 2.7.2 below.

Since the WHO/Enterprise Consultation, IVR has monitored the results of HIV vaccine trials and, following consultation with the WHO–UNAIDS HIV Vaccine Advisory Committee, issued statements to facilitate the interpretation of technical and safety aspects by national authorities.[36]

For more information, visit www.hivvaccineenterprise.org.

2.5.3 Malaria vaccine partnerships

IVR is a major partner of the Malaria Vaccine Initiative, coordinated by PATH, and participated with the Wellcome Trust and the Bill & Melinda Gates Foundation in the development of the ground-breaking Malaria Vaccine Technology Roadmap, officially released in Bangkok in December 2006 at the Sixth Global Vaccine Research Forum. The Roadmap is a global strategy that aims to develop a malaria vaccine by 2025 with a protective efficacy of more than 80% against clinical disease for at least four years. The strategy has 11 priorities covering areas ranging from vaccine discovery to policy and deployment.[37] IVR has also fulfilled the role of focal point for the "Malaria Vaccine Funders' Group",[8] whose participation and support were critical to the Roadmap process. The Funders' Group has called upon new and existing partners to work towards the realization of an effective malaria vaccine by acting on the priority areas of the Roadmap.

IVR has aligned its activities with the Roadmap priorities and acquired new funding for these, specifically for 'standardizing procedures to compare immune responses and clinical trial results by vaccine candidates' and for on-site clinical testing capacity. In addition, an editorial in the *Lancet*[38] commended the Roadmap, while underlining the critical need to build capacity in malaria endemic areas to carry out high-quality evaluation and testing of promising malaria vaccines.

For more information, visit www.malariavaccineroadmap.net.

2.5.4 The Global Partnership to Stop TB

Promoting partnerships and collaboration within the TB control and research communities is a central function of the Global Partnership to Stop TB. During the 2006–2007 biennium, IVR continued to serve as focal point for all vaccine-related activities within the Partnership and to act as Secretariat for its Working Group on New TB Vaccines. In an effort to align its operations with the objectives of the Global Plan to Stop TB 2006–2015,[39] the Working Group concentrated on five priority areas: (i) immune and functional markers of TB vaccine efficacy; (ii) TB vaccine trial end-points and diagnostic paradigms; (iii) new scientific approaches to keep the TB vaccine development pipeline filled; (iv) TB vaccine economics and product profiles; and (v) advocacy, communication and social mobilization related to TB vaccine development and introduction. Each priority area is represented by a small task force and many of IVR's activities are either executed by or performed in close connection

with these task forces. This new structure came into force at the end of 2006 and, by the end of 2007, most task forces had met and developed workplans to implement the objectives of the Global Plan to Stop TB.

For more information, visit www.stoptb.org.

2.5.5 Cervical cancer partnerships

IVR continued its collaboration with the International Agency for Research on Cancer, PATH, Harvard University, and the Institut Català d'Oncologia (ICO) on a multifaceted, five-year programme to support evidence-based decision-making on HPV vaccine introduction. This includes policy development, laboratory support, operational research on vaccine delivery and acceptability, economic analyses, the development of investment cases, and the collection and dissemination of data. In particular, IVR contributed to the establishment of the WHO/ICO Information Centre on HPV and Cervical Cancer, a web-based compendium of global, regional, and country-specific data, and on relevant prevention and control programmes that decision-makers can use to guide policy and practice on HPV vaccines. The data, which is collated from the most reliable sources of disease burden information, cover HPV prevalence, incidence, type distribution and cervical cancer related to HPV. The Centre incorporates new results as they are produced, with special attention to modelling studies that predict the impact of specific intervention strategies.

For more information, visit www.who.int/hpvcentre.

2.5.6 Pediatric Dengue Vaccine Initiative

IVR collaborates closely with the Pediatric Dengue Vaccine Initiative (PDVI) on the development and evaluation of dengue vaccines, and represents WHO on the PDVI Board of Counselors. Over the past biennium, collaboration focused on the harmonization of immunological readouts and on the development of clinical trial guidelines. Collaboration will also involve research on implementation issues related to future dengue vaccines.

For more information, visit www.pdvi.org.

2.5.7 Diarrhoeal and enteric disease partnerships

IVR is a strategic partner of the Rotavirus Vaccine Program (RVP), with CDC and PATH, for the evaluation of rotavirus vaccines in developing countries. Within this partnership, and with the collaboration of WHO regional offices, a series of meetings and training workshops were held to support the regional rotavirus surveillance networks. As a result of these efforts, over 55 countries in all regions are now conducting rotavirus surveillance using a standardized surveillance protocol and reporting system developed by WHO for hospital-based burden of rotavirus disease.[40]

For more information, visit www.rotavirusvaccine.org.

In addition, IVR has initiated a comprehensive study in Africa on the pre-emptive use of a cholera vaccine in vulnerable populations at risk in collaboration with the International Vaccine Institute and the Swiss Tropical Institute. This project, which will continue over 2008 and 2009, will gather evidence to facilitate the establishment of a potential stockpile of cholera vaccine for use in developing countries.

For more information, visit www.ivi.org/tr_chovi_program.html.

2.5.8 Measles Aerosol Project

Encouraged by published data showing the promise of aerosol delivery for measles vaccine, IVR, along with the American Red Cross and CDC, has been involved since 2002 in research to develop an alternative to injection methods for delivering measles vaccine. Critical to the success of the project has been the establishment of an efficient partnership with a large vaccine manufacturer and three leading device manufacturing companies. The strategic guidance provided by the partners in the Project, and scientific advice from its Product Development Group, have ensured the highest standards in the implementation of the activities. See Section 3.1.1 for details of the Project's achievements during 2006–2007 towards the licensing of an aerosolized measles vaccine.

For more information, visit www.who.int/immunization_delivery/new_vaccines/technologies_aerosol/en/index.html.

2.5.9 Meningitis Vaccine Project

The Meningitis Vaccine Project (MVP) is a partnership between WHO and PATH to eliminate epidemic meningitis as a public health problem in sub-Saharan Africa, where 430 million people are at risk of the deadly disease. The development of conjugate vaccines offers hope for a more effective prevention strategy against meningococcal disease in Africa. IVR's contribution has been key to ensure smooth collaboration among partners (WHO, PATH, vaccine manufacturer, trial sites, laboratories, ministries of health); adherence to international standards at all vaccine trial sites; in-country capacity-building and networks to conduct vaccine trials with the promotion of inter-site collaboration and strengthening of the regulatory capacity in African countries for the authorization of clinical trials. Activities of the MVP over the last biennium are described in this report under Sections 3.1.2 Meningococcal vaccine clinical trials; Section 3.5 discusses progress of the meningococcal carriage studies in Africa.

For more information, visit www.meningvax.org.

2.6 Ethical aspects of vaccine trials

Decisions on the approval and conduct of vaccine trials are difficult to make in an increasingly complex environment, coupled with a lack of scientific knowledge and track record on novel vaccine technologies and vaccination strategies. In order to be able to advise Member States and partners on sometimes contentious ethical,

regulatory and policy issues, IVR conducted extensive national and regional consultations with all stakeholders. Working with research agencies, trial sponsors, national regulatory authorities, ethics committees, decision-makers and community representatives, IVR and UNAIDS published guidance documents related to the preparation and conduct of prevention trials. Examples of this work are described in this Section and Section 2.7 on regulatory aspects of vaccine trials.

2.6.1 Access to care and treatment

Ethical principles of beneficence and justice combined with international human rights norms lay down certain obligations for researchers, sponsors and public health authorities. These include access to care, prevention and treatment for participants enrolled in vaccine clinical trials. However, these obligations are poorly defined in practical terms, inconsistently understood or inadequately applied. Guidance is thus clearly required on how to strike the right balance between the need to respect basic ethical and human rights principles, and the need to engage in research on new, life-saving technologies that may impinge on these principles.

"As scientific advances continue, WHO will be more proactive in leading a dialogue on setting priorities and ethical standards for research."

Dr Margaret Chan, WHO Director-General, Medium-term Strategic Plan, 2008–2013.

In 2006, IVR and UNAIDS completed a series of consultations in Africa, the Americas, Asia and Europe[41] to identify the nature of the guidelines needed; to review approaches being applied in practical field situations; and to define the level of obligations and constraints for providing care and treatment in the context of vaccine trials. As a result, a process – or framework – was formulated that considers the trial-associated populations under specific categories according to disease, and determines the standards of care for the related and non-related diseases and conditions. A list of questions aimed at acquiring the necessary background information relevant to the trial and the site for local decision-making accompanies the framework. This approach ensured that the key issues in determining appropriate care and treatment for trial participants would be considered in a structured, participatory and transparent way.

A discussion paper presenting the framework, published in *Vaccine*[30] in 2007, emphasized that, in most situations, no single country, industrial partner, sponsor or agency could or should bear the entire burden of providing treatment. Ad hoc partnerships should be formed to strengthen local research and health delivery infrastructures, and identify mechanisms and expertise to provide care and treatment for the disease under study, and beyond.

2.6.2 Inclusion of adolescents in HIV vaccine trials

The December 2007 WHO/UNAIDS AIDS Epidemic Update[42] showed that almost 50% of the 4.3 million new HIV infections in 2006 were among adolescents and young adults of 15–24 years of age, and half of these were girls and young women. Approximately 77% of girls and women infected globally live in sub-Saharan Africa,

where the major route of transmission is unprotected heterosexual exposure. Given the staggering scale of the epidemic in young people, a clear objective for any successful public health intervention to prevent HIV infection would be vaccination of adolescents with an effective vaccine before they initiate sexual activity, when their risk of exposure to the virus increases dramatically.

To discuss this challenge, IVR organized a consultation in Botswana in March 2006. Cosponsored by UNAIDS and the AAVP, participants considered the strategies and challenges of enrolling adolescents into HIV vaccine clinical trials to be conducted in developing countries, particularly in eastern and southern Africa. Approaches were identified that might resolve country-specific challenges related to the involvement of adolescents in vaccine trials. Recommendations were made on the four major topics discussed, namely: (i) criteria for product selection and clinical trial design; (ii) ethical and legal issues; (iii) community acceptance and participation; and (iv) regulatory considerations. The executive summary and recommendations were published as a position paper in *AIDS* in 2007,[28] in order to reach the general clinical, scientific and regulatory community involved in the review, approval and monitoring of clinical trials and potential licensing of HIV vaccine candidates. The recommendations were further discussed and endorsed by the WHO–UNAIDS HIV Vaccine Advisory Committee which met immediately after this consultation.

2.6.3 Ethical considerations in biomedical prevention trials

International documents such as the Helsinki Declaration and the Guidelines of the Council for International Organizations of Medical Sciences (CIOMS) provide general statements and principles on various ethical aspects of conducting research in human subjects. However, they lack practical guidance on how to implement these principles, in particular in resource-limited countries and in the context of implementing multinational collaborative research projects or clinical trials. To bridge this gap, UNAIDS had issued a guidance document on "Ethical considerations in HIV preventive vaccine research". However, in the seven years since its publication in 2000, significant changes have affected the conduct of trials with novel biomedical interventions, including vaccines, microbicides, circumcision and post-exposure prophylaxis. The standards and quality of care and treatment available through national AIDS prevention and control programmes have considerably improved, with a growing number of people from resource-limited countries having access to antiretroviral treatment. New national and international policy documents have also been published that address contentious and sensitive issues surrounding the conduct of clinical trials, such as the involvement of women and adolescents.

To reflect these changes, IVR and UNAIDS established an international working group of leading experts in the areas of ethics and clinical trials, along with community representatives, to revise the original document. The group carried out an extensive

analysis of all relevant material published since 2000 for the new UNAIDS/WHO guidance document on ethical considerations in biomedical HIV prevention trials, published in 2007 in English, French, Portuguese, Russian and Spanish.[43] Moreover, these new guidelines will form the basis of a training module for workshops to familiarize national ethics committees, regulatory agencies, principal investigators and community representatives with basic ethical principles and how to implement them in practice.

2.7 Regulatory aspects of vaccine trials

2.7.1 Novel strategies to test HIV vaccine efficacy

While Phase I and II clinical trials are primarily concerned with the safety and immunogenicity of candidate vaccines, Phase III pivotal trials are intended to assess the protective efficacy and safety of a vaccine in populations for whom the vaccine was designed, and to provide the basis for regulatory rulings concerning licensure or approval to market the vaccine. However, the decision to move candidate vaccines from Phase II to Phase III trials is fraught with scientific, logistic and financial challenges. The major scientific challenge remains the lack of knowledge on the quality and quantity of immune responses required for protection against infection or development of disease. In addition, prior to the conduct of a licensure trial, considerable time and resources are required to develop definitive manufacturing processes, fully validate methods for the analysis of laboratory samples and data, and create extensive trial site infrastructures. These costs are over and above the massive investment needed to run the trial itself from sponsors, clinical researchers and communities. There is, therefore, an understandable reluctance to embark upon pivotal Phase III trials without evidence that the vaccine is likely to demonstrate a significant level of efficacy.

To address some of these challenges, an additional vaccine evaluation step – a Phase IIB Test-of-Concept (Phase IIB-TOC) trial – has been proposed as a bridge in the development and evaluation process between Phases II and III trials. This approach has already been used to some extent with several vaccines, as well as in the current HIV microbicide trials.[44]

A consultation, convened by IVR, UNAIDS and IAVI in New York in February 2006 explored the potential role and position of Phase IIB-TOC trials in the overall continuum of HIV vaccine development. Based on the outcomes of this consultation, a position paper was developed and published in the journal *AIDS* in 2007,[29] which provides insight for vaccine developers, national regulatory authorities, ethical committees, scientists, clinicians, and community representatives to understand better the implications related to introduction of this new strategy for testing candidate HIV vaccines.

2.7.2 Definition of HIV vaccine efficacy based on surrogate markers

As a result of the WHO/Enterprise Consultation in March 2007 (see Section 2.5.2) IVR organized an international expert group meeting in Paris in September 2007 in collaboration with the Agence nationale de Recherches sur le SIDA (ANRS) and the Bill

& Melinda Gates Foundation. The major issue on the table was whether the measurement of viral load was a useful surrogate marker to determine HIV vaccine efficacy. The meeting was attended by experts from major regulatory agencies, including those from developing countries, clinicians, principal investigators, statisticians, ethicists, community representatives and members of the WHO–UNAIDS HIV Vaccine Advisory Committee. Representatives from the pharmaceutical industry also contributed as observers to the technical discussions. The report and recommendations will by published in the journal *AIDS* in 2008.

2.7.3 Standardization of HIV neutralization assays

In 2006–2007, IVR cosponsored an international collaborative project with the European Commission on "Standardization and comparative evaluation of assays for measurement of anti-HIV neutralizing antibodies". Twelve laboratories from Africa, Asia, Europe and the USA participated in the project. Six different assays for HIV neutralization were comparatively evaluated using standardized panels of monoclonal neutralizing antibodies, pools of polyclonal plasma and a reference panel of HIV isolates with different neutralization sensitivity. Important scientific findings of the project included recognition that no single assay could reproducibly detect neutralization of all HIV isolates, in particular primary HIV isolates which represent a major target for HIV vaccines. The standard operating procedures and reference reagents developed as a result of this project will be distributed broadly through the WHO Repository.

In March 2007, IVR presented the outcomes of this project to an expanded scientific meeting with the participation of VAC members, the technical report of which is in press.

2.7.4 Immune testing platform for malaria vaccines

The development and harmonization of an immune testing platform for malaria vaccine trials focussed on optimizing and harmonizing assays; and producing standard malaria immune reference sera.

As part of these activities, IVR convened a network of groups involved in both assay conduct and evaluation of results. A Global Assay Harmonization Work Plan was formulated to optimize and standardize the conduct and analysis of selected assays for malaria vaccines; a standard reference reagent was made available; and funding for start-up activities secured. These activities were developed following a framework of assay harmonization and standardization that is consistent with potential regulatory expectations.

The results of this work will lead to standardized procedures to compare immune responses and clinical trial results of vaccine candidates, as well as criteria for the rational selection of candidate vaccines, which are two Roadmap priorities. More broadly, these efforts should advance the state-of-the-art of vaccine development

through (i) improved screening and down-selection of multiple candidate vaccines at preclinical and early clinical stages; (ii) a better understanding of potential correlates of protection; and (iii) increased consistency in intra- and inter-laboratory performance, and thus more dependable assay comparison.

2.7.5 Markers and assays of TB vaccine efficacy

IVR's efforts to identify markers of TB vaccine efficacy largely focused on obtaining consensus on the use of harmonized and standardized laboratory assay protocols. IVR also investigated the appropriateness of both new assays and those in current use.[45] As a result of this analysis, many of the newer immune assays were deemed impractical for use in an efficacy trial situation. Nonetheless, participants at a workshop held in November 2007 decided that introduction of a functional assay, i.e. one based on *Mycobacteria*-infected host cells as a source of antigen, might yield valuable additional information and therefore be desirable. Since these assays are not readily reproducible, a collaborative feasibility study will be launched in 2008 to overcome this hurdle.

2.7.6 Analysis of correlates of protection for dengue vaccines

In 2007, IVR published a review that elaborated the scientific basis for establishing correlates of protection for dengue vaccines. While stressing the importance of neutralizing antibodies, the review also underlined the differences between dengue and other flavivirus vaccines.[46]

There are now a variety of dengue vaccines in various stages in the developmental pipeline. In an attempt to make inter-laboratory information more directly comparable, IVR and PDVI initiated a programme to harmonize the procedures used for the plaque reduction neutralization test (PRNT). This test is the most common assay used to measure neutralizing antibody. The presence of antibody is believed to be most relevant for determining protective anti-dengue virus immunity. While other neutralizing antibody assays are being considered for use in large-scale vaccine field trials, the PRNT is still considered the laboratory standard against which other neutralizing antibody assays should be compared.

IVR also conducted a collaborative study to establish a reference panel of dengue infection-immune sera. These data revealed considerable inter-laboratory variability due to the different methods employed to perform and analyse the PRNT data, corroborating the need to establish a more harmonized approach to dengue virus PRNT. This resulted in the publication of guidelines for plaque reduction neutralization testing of human antibodies to dengue viruses.[47]

2.7.7 Post-marketing surveillance for rotavirus vaccines

A meeting on post-marketing surveillance for rotavirus vaccines was coordinated by IVR with the Global Advisory Committee on Vaccine Safety in December 2006 to

address specific safety aspects of rotavirus vaccines. After reviewing the data on intussusception generated by pharmaceutical companies in their clinical development of rotavirus vaccines and conducted in large study populations of > 60 000 each, the Global Advisory Committee on Vaccine Safety recommended that post-marketing surveillance was required to evaluate the safety profile. Participants reviewed the generic protocols for rotavirus vaccine safety with respect to intussusception, being developed by WHO and Murdoch Children's Research Institute in Australia, and for vaccine impact, developed by CDC. In the coming years, these protocols will be deployed in countries where rotavirus vaccine is being introduced in order to document both the safety and effectiveness of the vaccine.

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3 Research and product development for priority new vaccines and technologies

The scope of product research and development is as vast as it is diverse. Furthermore, today's vaccine development world is no longer confined to the private sector, but comprises a wide range of players that are helping to accelerate the availability of new vaccines. IVR maintains its involvement in research and development for innovative products in this new environment, as these activities help develop vital tools for WHO's immunization programme, particularly in developing countries. In partnership with both the public and private sectors, IVR may therefore identify the need for a new or improved vaccine technology, or lead or partner with a development effort in this field. Moreover, in order to continue providing meaningful assistance to its partners in this area of work, it is considered essential that IVR staff maintains its competency in product research and development through hands-on involvement.

The development of a meningitis vaccine to fight epidemics in sub-Saharan Africa is a good example where IVR had identified the need and designed the project for this neglected disease. In these cases, the project is initiated and pursued until a group is identified to take over or share the major responsibility for its success. In a few, specific instances, it is considered appropriate that IVR takes responsibility for a product development project, such as the aerosolized measles vaccine.

The majority of IVR's research and product development activities, however, aim to "encompass" ongoing efforts, i.e. to take responsibility for a part of the research that falls within the mandate and comparative advantage of WHO. Participating in clinical study design, providing guidelines and strengthening trial sites are priority IVR activities that use limited resources in the most efficient way.

In the coming years, IVR will complete the projects it is currently undertaking and demonstrate the impact of new products on global public health. It will also remain vigilant, active and open to the future needs of product research and development in developing countries.

3.1 Product development

3.1.1 Measles aerosol vaccine

The current safe, effective and inexpensive measles vaccine is administered through intramuscular injection. In recent years, outstanding progress in measles mortality reduction has been made as a result of an effective strategy. However, under-utilization of measles vaccine is a major reason for the remaining disease burden. Novel technologies, which allow the administration of vaccines without specialized training and which could, in avoiding injections, offer an even larger measure of safety in low resource conditions, represent an exciting frontier in research.

Aerosol delivery is the most promising non-injectable method of measles vaccination studied so far, and its efficacy is thought to be comparable to that of injected vaccine. Administration of measles vaccine by the respiratory route mimics natural infection with measles.

In April 2006, the testing of the three candidate vaccines (vaccine and delivery device combinations) in a GCP compliant Phase I clinical trial started at three sites in India. These parallel clinical trials to evaluate safety and immunogenicity in Kolkata, Pune and Chennai, each with a different nebulizer in 180 healthy measles immune individuals (1–35 years of age) should be completed during 2008. In the group aged 18–35 years, sixty volunteers have received the vaccine according to schedule. Preliminary results confirmed good immune response after measles aerosol vaccination. No severe or serious adverse events were reported after 365 days of follow-up.

Upon an unexpected observation of increased eosinophil cell counts following immunization in one group of volunteers, and at the recommendation of the Data Safety Monitoring Board (DSMB), an additional protocol to compare the safety profile, eosinophil cell counts and IgE levels among twenty vaccinees receiving either the subcutaneous or the aerosol measles vaccine was conducted in Kolkata in early 2007. Since the results reported no statistically significant differences between the two vaccine groups, the DSMB approved continuation of the original Phase 1 study in the Spring of 2007. Follow-up and enrolment of other age groups is ongoing.

Results in all three sites showed that geometric mean antibody concentrations increased significantly from day –30 to day 28. Results to date using PRNT and ELISA show that while volunteers with higher pre-vaccination levels had higher post-vaccination levels, increases from pre- to post-vaccination antibody titres were greater in those that had lower pre-vaccination antibody levels.

3.1.2 Meningococcal vaccine clinical trials

IVR activities within the Meningitis Vaccine Project contributed to the following results, bringing us closer to an affordable, life-saving vaccine against meningococcal disease.

PHASE I, DOUBLE-BLIND, RANDOMIZED TRIALS IN INDIA

Phase I, double-blind, randomized trials in India showed the vaccine to be safe and immunogenic. In preparation for further studies, IVR, PATH and partners carried out two fundamental activities, namely a joint regulatory review of clinical trial applications, conducted by regulators from five African countries, and an inter-site workshop to facilitate collaboration and uniformity among sites and to exchange experiences in the field, both held in the Gambia in June 2006. Topics included pre-recruitment methods, increasing community involvement and understanding of clinical studies, the informed consent process, how to improve compliance with blood sampling, procedures for the presentation of results to the community, and career path issues for field workers.

PIVOTAL PHASE II STUDIES IN AFRICA

A total of 601 children aged 12 to 23 months were recruited in the Gambia and Mali for this pivotal Phase II study. A major milestone was reached with the release of the

week 4 results of this study,[1] showing the vaccine to be safe and immunogenic. Indeed, at this evaluation point, the conjugate product elicited bactericidal antibody titres almost 20-fold higher than the current licensed tetravalent polysaccharide vaccine. This high response could be a good predictor of the ability of the conjugate vaccine to induce long-lasting immunity. The results of this Phase II clinical study makes possible initiation of the Phase II/III study in the older age group (2 to 29 years) of the target population, as well as a Phase II study in infants. Thus, although further rigorous development of this vaccine is needed, there is now great optimism that a highly effective tool to prevent epidemic meningitis will finally become available in the foreseeable future.

"This important study brings real hope that the lives of thousands of children, teenagers, and young adults will be saved by immunization and that widespread suffering, sickness and socioeconomic disruption can be avoided", said Dr Margaret Chan, WHO Director-General, at the release of the latest data in June 2007.

In November 2006, two months after the trial started, an investigational GCP audit was conducted at each study site as part of the overall MVP audit programme. In January 2007, a Joint GCP Regulatory Inspection of site facilities, procedures and study documentation took place at the site in Bamako in Mali. The inspectors – national regulatory authorities from five African countries, WHO facilitators and an external expert – commended the high quality of the trial, which was adhering to international standards and recommendations, and raised valuable points for improvement.

PHASE II/III TRIALS IN AFRICA AND ASIA

Similar to the Phase II pivotal study described above, IVR contributed to the essential preparation for the Phase II/III clinical trials at three sites in Africa (the Gambia, Mali and Senegal) and one site in Asia (Vadu district in Maharashtra, India). Firstly, IVR, PATH and partners organized two inter-site training workshops in Mali to ensure collaboration and uniformity among sites. In March 2007, one workshop focused on harmonizing on-site standard operating procedures, while a second workshop in May 2007 concentrated on how to assess meningococcal carriage. Following these workshops, IVR promoted the conduct of a joint regulatory review of the clinical trial applications by regulators from four African countries, at a meeting facilitated by IVR in Senegal in June 2007. Questions and suggestions formulated during the review process helped improve the study protocol.

The recruitment was completed at all four sites in August 2007. Two months into the trial, an investigational GCP audit was carried out at each study site as part of the overall MVP audit programme. All trial sites were found to be proceeding satisfactorily.

Finally, the Phase II infant study protocol was finalized after an extensive peer review process, and has entered the ethical and regulatory clearance process.

In the coming biennium, IVR will continue the above activities within the MVP partnership, with priority focus given to coordinating the identification of study sites in Africa and in India for additional clinical trials, as well as coordinating the conduct of these studies.

3.1.3 Murine rabies monoclonal antibody cocktail for post-exposure treatment

The need to replace rabies polyclonal immunoglobulins as an essential component of rabies post-exposure prophylaxis is widely acknowledged. A study to discover a unique combination of murine anti-G monoclonal antibodies (Mabs) from available panels for broad use in developing countries at low cost concluded that monoclonal cocktails do provide significant protection. In some cases, protection was higher than that provided by human immunoglobin (HRIG) and, most interestingly, one cocktail provided 100% protection in experimental animals. The study concluded that although a number of other projects aiming to develop Mabs for rabies post-exposure prophylaxis are ongoing, the WHO study presents quality outcomes and thus promising conditions for partnerships with developing country industrial partners to develop the product further for public sector use.

3.1.4 Upstream rotavirus vaccine candidates

Triggered by a global consultation convened by IVR in March 2006, a new initiative was founded by the Bill & Melinda Gates Foundation for alternative rotavirus vaccine candidates. This specialized meeting also led to a call for proposals by IVR and the award of a research grant to Murdoch Children's Research Institute in Australia to look at formulations and buffers for live oral rotavirus vaccines. A follow-up meeting in November 2007 considered the clinical trial implications for the new alternative rotavirus vaccines.

In addition, IVR supported technically and financially the further development of the neonatal rotavirus vaccine candidate RV3, within its collaboration with Murdoch Children's Research Institute and BioFarma, Indonesia. It also supported the establishment of a project to investigate the immune correlates of protection for rotavirus infection.

3.1.5 New technologies: needle-free intradermal delivery of reduced-dose vaccines

Intradermal administration of vaccines offers several advantages over intramuscular or subcutaneous administration:

- A lower dose is required for vaccines such as influenza, hepatitis A, hepatitis B and for rabies where reduced-dose intradermal delivery is now the norm in many countries. This can potentially reduce the cost of immunization, as well as enhance access where production capacity is limited.
- It is safer – if administered with an appropriate device – as it avoids the risk of injury to nerves, veins and bones. In addition, depending on the device used, the risk of needle-stick injury may be reduced or eliminated. These advantages could facilitate immunization in resource-poor settings.

On the other hand, existing intradermal delivery with needles and syringes is technically complex and unreliable. A number of new injection technologies have been developed to make administration by this route safer and more reliable. One of these technologies – needle-free intradermal jet injection – was shown to be able to deliver intradermal vaccines reliably and with minimal training, based on an IVR evaluation of needle-free jet injectors.

In order to investigate the utility of intradermal delivery for dose reduction, and to assess the field usability and patient acceptance of this needle-free intradermal device, IVR, in collaboration with the WHO Polio Eradication Initiative and CDC, undertook the following clinical trials:

- Inactivated polio virus (IPV) was administered intradermally by jet injector in two Phase II clinical trials in infants: one in Cuba and one in Oman. In both studies, the reduced dose (0.1 mL) administered intradermally was compared to the full dose delivered intramuscularly.
- Influenza vaccine was administered to toddlers in a Phase I/II trial in the Dominican Republic. The reduced dose administered intradermally by jet injector was compared to both the reduced dose and to the full dose delivered intramuscularly.

Results for all three trials are expected in early 2008.

3.2 Support to clinical evaluation

All vaccine trials should be conducted at the highest scientific and ethical standards, and meet Good Clinical Practice (GCP) and applicable regulatory requirements. The capacity to respect these standards, particularly in institututions based in disease-endemic areas, is often lacking. While IVR is not a training unit *per se*, it actively carries out activities to assess and strengthen clinical trial sites for the evaluation of vaccine candidates, notably by conducting GCP and ethics training for vaccine trial staff; and by ensuring high-quality safety and clinical monitoring of the trials, including training for clinical monitors. Through this activity, the required international standards are met for all clinical evaluation projects that receive IVR support, and the confidence and capacity strengthened of local institutions to conduct trials.

3.2.1 Clinical trials of HIV vaccines

ASIAN REGIONAL NETWORK IN SUPPORT OF HIV VACCINES

Following the example and positive experience of the AAVP (see Section 2.5.1), IVR, in collaboration with IAVI and the Global HIV Vaccine Enterprise, facilitated the conduct of a regional consultation on "Approaches to the development of an Asian Regional Network in Support of HIV Vaccine Trials" in November 2006. The consultation concluded that prevalent epidemiological patterns in Asia would make it very difficult to conduct an efficacy trial with HIV vaccines within a single Asian country. An alternative would be to conduct transnational multi-centre trials, although

this would pose a number of challenges related to the need for common immunological platforms at multiple sites. These should be harmonized with regard to national policies, ethical, regulatory, legal and community frameworks. The recommendations of this consultation are being discussed by individual countries in order for specific recommendations to be made at the next regional meeting in 2008.

DEVELOPMENT OF AN IMMUNOLOGICAL PLATFORM FOR TESTING HIV VACCINES

In 2006 and 2007, IVR organized two technical training workshops on "Applications of novel immunological assays to measure anti-HIV specific immune responses in HIV vaccine trials" (Dakar, December 2006 and Johannesburg, November 2007). These workshops were conducted in collaboration with the US National Institutes of Health, the HIV Vaccine Trials Network, Duke University (USA) and the National Institute of Virology and Infectious Diseases of Johannesburg. The participants for this training were selected through an open call for applications from young African scientists involved in relevant vaccine research and clinical trials. As a result, more than 30 young scientists from 16 African countries received training in implementation of new laboratory techniques for evaluation of humoral and cellular immune responses.

3.2.2 Standard definitions and clinical trial design for malaria vaccines

IVR activities in this area concentrated on developing and documenting definitions and methods to measure the clinical outcomes of malaria vaccine trials, so that data can be compared across clinical sites and preparatory surveillance studies.

The initial work focused on developing guidelines for case definitions of uncomplicated and severe malaria for use in efficacy trials of advanced malaria vaccines. IVR convened a study group that developed and harmonized these case definitions, provided guidance on optimal trial design, and recommended methods of measurement and analysis. A summary report was published on this topic,[2] which has helped to inform discussion on the clinical evaluation of the leading malaria vaccine candidate among developers as well as regulatory authorities. In addition, a more extensive guidance document with proposed protocols or algorithms for case definitions and trial design issues is in preparation.

In collaboration with the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, IVR has also strengthened the clinical trial site in Shanghai, China to conduct a Phase I trial of a *Plasmodium falciparum* MSP-1/AMA-1 chimeric protein (PfCP-2.9). The trial and activity was completed in March 2007.[3] The capacity of the Ethical Committee of Shanghai Hospital to conduct an ethical review of a clinical trial was also assured.

3.2.3 Clinical trials of new TB vaccines

IVR's work on TB vaccine clinical trials has two arms: one focuses on end-point definitions and diagnostic paradigms, and the other provides support to individual sites

through the clinical trialist network. This network met for the first time in November 2007, with participants from India and several African countries. It was decided that, as a first practical step, standard operating procedures for field work should be shared and implemented at different sites before the development and implementation of efficacy trial protocols.

Progress towards the harmonization of clinical end-points and diagnostic paradigms included the preparation of discussion papers on (a) trial end-points in paediatric and adolescent TB vaccine trials; (b) standardization of diagnostic tools for use in TB vaccine trials; and (c) a diagnostic algorithm for use in paediatric vaccine trials. These documents will form the basis of a "White book on clinical end-points for TB vaccine efficacy trials" to be published in 2008.

3.2.4 Clinical evaluation of dengue vaccines

IVR promotes the development of dengue vaccines mainly through the provision of technical support for vaccine evaluation. Much of this work is conducted in partnership with the Pediatric Dengue Vaccine Initiative (PDVI). Extensive consultations were held to produce a guidance document on the clinical evaluation of dengue vaccines in exposed populations. The guidelines propose, inter alia, specific clinical end-points, requirements for case detection, and a stepwise approach towards safety evaluation of dengue vaccines. The document was reviewed by the WHO Expert Committee on Biological Standardization in October 2007 and will be published in early 2008.

3.2.5 Clinical trials of rotavirus vaccines

Enrolment of subjects in a WHO rotavirus vaccine trial in South Africa to assess the safety, reactogenicity and immunogenicity of the GlaxoSmithKline Rotarix™ vaccine in HIV-infected infants was completed, and the final study results are expected in mid 2008.

The WHO/PATH sponsored and coordinated Phase III trials in Malawi and South Africa both completed enrolment, and study surveillance was carried out to measure efficacy over two rotavirus seasons. The results of these trials should be available by the end of 2008.

3.2.6 Training in GCP and GLP: measles aerosol vaccine trials

Major challenges for the Measles Aerosol Project included ethical and regulatory issues related to carrying out research in a developing country setting. Considerable capacity building was therefore provided at the clinical sites, at the laboratories and with ethical review committees to ensure that the trials were conducted according to international standards. In addition, given the paucity of regulatory guidance on combination products (vaccine and aerosol delivery devices), numerous expert consultations and the development of new assessment methods were necessary to complete the IND dossier. To ensure GCP and GLP compliance during the Phase I trial in India, IVR coordinated the following tasks over the past two years:

- An evaluation of the clinical trial sites and testing laboratories;
- Practical training in international GCP procedures and methods at workshops for the staff of the pre-selected trial sites;
- Training of local ethical committees of these sites on the updated Indian Council of Medical Research guidelines for ethical review committees;
- GCP training of the full clinical study team of the three sites prior to the start of the trials; and
- Standardization and quality assurance of laboratories and testing of the standard operating procedures, with the support of the Global Measles Specialized Laboratory (Health Protection Agency, UK).

An experienced GCP field coordinator was appointed to assist the research teams with the preparatory work leading to the start of the trials, and two WHO-appointed trial monitors conducted the monitoring visits at the three sites.

Lastly, compliance with GCP standards was documented by the conduct of two Independent External Audits (IEA) of the three clinical sites, the data management centre and the PRNT laboratory in March and April 2007, and in October and November 2007. The audits reviewed the procedures, equipment, facilities and quality of essential documents maintained, and assessed compliance with the trial protocol, standard operating procedures, ICH-GCP, GLP, WHO guidelines and any other applicable regulatory requirements. Although the initial IEA identified some major observations at each site, the most recent IEA confirmed that the joint capacity-building efforts of the Indian Council of Medical Research and WHO were very successful, since all the sites involved in the trial are now compliant with these international standards.

3.2.7 Facilitating clinical trials of meningococcal conjugate vaccine in Africa

To enhance national regulatory capacity in African countries for the licensure/marketing authorization of vaccines, IVR contributed to the African Vaccine Regulators Forum, and supported regulatory reviews of clinical trial applications and regulatory GCP inspections. In the next biennium, activities will focus on bridging the gap between vaccine development and vaccine introduction. Specifically, IVR will hold a scientific workshop on "Vaccine Development from Bench to Licensure: a Meningococcal A Conjugate Vaccine for the African Meningitis Belt", and coordinate the dissemination and publication of papers presented at the meeting. The expected outcome will be improved knowledge and expertise among participants on vaccine development; increased interaction between investigators and partners; and a compendium of papers on issues and lessons learnt on product and clinical development, regulatory strategies, serology and data analysis, and partnership building.

3.2.8 Training in vaccinology

IVR scientists contributed to the annual WHO training course in Immunology for developing country researchers and health professionals by providing training in a range of topics related to vaccinology. IVR staff also played a role in numerous other courses for developing country scientists, including the Advanced Vaccinology Course in Annecy, France, and the IVI-sponsored International Advanced Course on Vaccinology for the Asia Pacific Regions, held each year in Seoul, Republic of Korea. The week-long training in May 2007 brought together nearly 100 people from 26 countries to help them cope better with the threat of infectious diseases, including emerging diseases such as avian influenza.

Research and Product Development References

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3 Qingfeng Zhang et al. Construction and evaluation of a multistage combination vaccine against malaria. *Vaccine*, 2007, 25(11):2112–19.

4 Implementation research and development of tools to support evidence-based decisions

The importance of implementation research is highlighted in the Global Immunization Vision and Strategy 2006–2015,[1] and relates directly to the programmatic goals of reaching more children, adding new vaccines into immunization programmes, and moving beyond infant immunization into childhood and adolescent schedules for a number of vaccines. The potential areas of research are many and thus, in line with its mission and a rigorous prioritization process, IVR focuses on:

- Research that facilitates the continuing evolution of immunization programmes, in particular as related to immunization schedules;
- Research to build the technical evidence base for the optimal use of vaccines, including the generation of data, tools and practices;
- Research to bridge the "knowledge–action" gap between product development and vaccine use, and how policy implementation and decision-making could be made more efficient.

While continuing work on the above priorities, the strategic orientation for the coming biennium will increase its focus on alternative vaccine delivery strategies. This area is very pertinent in the evolving vaccine landscape, and will affect the inclusion of new vaccines such as HPV into immunization programmes, and vaccines used in campaign settings. IVR's work on immunization schedules is also intimately linked with vaccine delivery strategies.

4.1 Development of tools for evidence-based decision-making

Decision-making about immunization takes place at all levels – individual, community, national, regional and global – and the needs at these levels may be different. One role of IVR is to ensure that the necessary data, tools, and models are available at each level to facilitate evidence-based decisions. To strengthen its existing activities in this area, IVR established a new advisory group on Quantitative Immunization and Vaccine Research (QUIVER). Endorsed by the WHO Strategic Advisory Group of Experts on immunization, the group replaces previous ad hoc expert meetings and advises on research issues related to:

- Estimating the burden of vaccine-preventable disease;
- Modelling vaccine interventions;
- Economic evaluations of vaccines, immunizations and related technologies and interventions; and
- Analytical components of operational and implementation research.

The first meeting of QUIVER, held in September 2007, reviewed methods for estimating neonatal tetanus and measles disease burden, strategic planning tools for measles, and guidelines for economic evaluations. Members also assessed the

responses received to requests for proposals to evaluate global disease burden and model potential uses of influenza vaccines.

IVR's work on evidence-based decision-making spans several areas. These include setting norms and standards for evidence; systematic reviews to gather the best available evidence; and the development and field-testing of tools to facilitate the decision-making process. IVR has worked closely with other teams in the Department of Immunization, Vaccines and Biologicals, as well as with the Bill & Melinda Gates Foundation, to foster a culture of national immunization technical advisory groups (ITAGs) in developing countries. It is expected that the ITAG can ensure maximum use of these norms and standards, and the global databases and tools, in their national immunization programmes.

The following sections highlight examples of IVR's work in this area during 2006–2007.

4.1.1 Measles Strategic Planning tool

Despite the success of immunization programmes in reducing measles mortality globally by 68% between 2000 and 2006, the disease remains a leading cause of vaccine-preventable deaths. WHO and UNICEF are working with CDC and other immunization partners to meet a global goal set out in the Global Immunization Vision and Strategy: a 90% reduction, from 2000 levels, in measles mortality by 2010.

As part of this global effort, countries are being asked to develop five- and ten-year plans of action for measles control in their immunization multiyear plans. In order to do this, they must assess national measles epidemiology and current measles vaccination coverage, and consider other health interventions that could be bundled with measles vaccination. This approach will lead to sound strategies that combine elements of routine and supplemental immunization activities to reduce or eliminate measles.

IVR has created a comprehensive Measles Strategic Planning (MSP) tool, which uses a quasi-dynamic model of measles epidemiology, implemented in Excel spreadsheets (Table 2), to help countries develop measles vaccination strategies. Using data provided by countries, the application compares the impact of various measles vaccination strategies in terms of number of people susceptible to measles as well as the costs and cost-effectiveness of the strategies. To assist national immunization managers and in-country staff to use the MSP tool to choose the most appropriate measles vaccination strategy, given limited resources, IVR is working with CDC, PATH and the Stanford University Medical Media and Information Technology group to develop an e-learning module, called *Strategic Planning for Measles Control*. The module will be disseminated through PATH's Advanced Immunization Management e-learning platform, which provides national immunization managers, in-country and global partners with the tools and guidance needed to make informed decisions on vaccine introduction and immunization

financing. These activities facilitate the objectives of national programmes as well as those of the GAVI Alliance. (See also Section 4.2.1. on the application of the MSP as a tool to estimate measles disease burden.)

TABLE 2. MODEL OF PARAMETERS TO BE SET BY MSP TOOL USER

PARAMETERS TO BE SET BY USER:		
Case Fatality Rate (CFR) among children 1-4 years	3%	?
Coverage Improvement Rate (CIR)	1.025	?
Maximum value for routine coverage	99%	?
Catch-up measles campaign: Year of campaign	2006	?
– Minimum age of catch-up target group	0.75	?
– Maximum age of catch-up target group	14	?
Routine 2nd dose: Year of introduction	2010	?
Routine 2nd dose: Age of vaccination	2	?
Follow-up measles campaign: Year of 1st campaign	2009	?
– Minimum age of follow-up target group	0.75	?
– Maximum age of follow-up target group	4	?
– Follow-up campaign interval (in years)	3	?
– Last year of follow-up campaign	2026	?

4.1.2 Economic evaluations of vaccine-preventable diseases

One of the strategic areas of IVR's implementation research in low- and middle-income countries is to assess vaccine-preventable disease burden, to estimate and model vaccine impact and to determine the cost-effectiveness of immunization interventions through the use of standard methods.

To address perceived deficiencies in the methodology of published studies on economic evaluations of immunization programmes, IVR developed guidelines to

improve and standardize how they are conducted in order to facilitate comparison between studies. The economic guidelines provide clear, practical, high-quality indications for those who conduct economic evaluations to meet the needs of decision-makers for relevant, reliable and consistent information. IVR commissioned the guidelines in early 2006, which were then peer reviewed by experts in health economics, mathematical vaccine modelling, public health and vaccines, among partners in academia and international health. These experts were first convened at an ad hoc expert meeting on "Standardization of economic evaluations of vaccine-preventable diseases" in March 2007, and the guidelines endorsed with minor modifications by QUIVER in September 2007.

The primary audience of the guidelines are economists and health service researchers in the public and private sectors who conduct and critically appraise economic evaluations of vaccine-preventable diseases at any level. The secondary audience are programme staff who use cost-effectiveness information to aid those who make decisions on the funding of immunization programmes. Programme staff at the country level will be able to use these guidelines to assess the transparency, completeness and comparability of economic evaluations that have been conducted for their own country, or for countries in their region. A third audience are agencies such as the GAVI Alliance, the Bill & Melinda Gates Foundation, WHO, UNICEF and international development agencies that sponsor and commission economic evaluations. This audience may use the guidelines as a basis for the terms of reference of future economic evaluations.

The guidelines should strengthen IVR's coordinating role in collating essential data and in designing tools to support national decisions on prioritization, use and optimization of new or under-utilized vaccines and technologies. In addition, the guidelines redress the current limitations of evaluations and will thus ensure better results that are useful for both international and national priority setting. This said, the possibility of bias cannot be completely eliminated given the inherent judgements pervasive in the conduct of economic evaluations.

In order to disseminate the guidelines, to be published in early 2008, for country-level use, IVR has embarked on a project with the London School of Hygiene and Tropical Medicine (LSHTM) entitled "Online International Vaccine Economics" (OLIVEs). This web-based 'proof-of-concept' data repository builds on existing resources and competencies of the National Centre for Health Outcomes Development at the LSHTM and will allow a much broader access to the guidelines. The data repository will have a dedicated focus on vaccine economics, and provide on-line access to the latest statistics required to perform comparative country-specific economic evaluations, including those on vaccine timeliness.

4.1.3 Planning for TB vaccine introduction

Experience in introducing new tools – and vaccines in particular – to control communicable diseases has shown significant delays between the licensure of a product and its availability at country level. Therefore, IVR together with the three Stop TB working groups on new vaccines, new drugs and new diagnostics, initiated a process to encourage policy-makers and practitioners at the global and national levels to accelerate the introduction of these technologies into the respective public health programme. To this end, a "retooling" framework for new tools in the fight against TB was developed, comprising the elements (a) systemic and programmatic readiness for change; (b) adoption and development of new policy; and (c) introduction and implementation of new tools.[2]

4.2 Disease burden estimation

4.2.1 Measles

Despite the global progress in measles surveillance and reporting, complete and reliable surveillance data on the number of measles deaths are lacking in many countries, particularly those with the highest disease burden. Moreover, as surveillance data do not allow direct measurement of global measles mortality, models continue to be used for this purpose. Since 2003, WHO has been using a method to estimate measles mortality based on a natural history approach.[3] The results from this model are expected to become less robust as measles incidence declines.

To improve the estimation of global measles disease burden, and to allow country-specific evaluations that can be used to modify measles mortality reduction strategies, WHO published an updated version of this model[4] in 2007, that looked at whether the measles mortality reduction goal for 2005 had been achieved. With this updated model, IVR estimated measles mortality for the year 2006 using (i) the most recent time series of population data through 2006; (ii) WHO/UNICEF routine vaccination coverage estimates and reported vaccination coverage from Supplemental Immunization Activities (SIA)s; and (iii) country-specific measles incidence as reported to WHO for selected countries based on assessed quality of surveillance.

This analysis was reviewed by the Quantitative Immunization and Vaccine Research expert panel, who considered the cohort modelling approach of the Measles Strategic Planning tool to be superior to the static model for estimating trends in measles mortality, as it uses 1-year instead of 5-year age groups and approximates the effect of herd immunity.

After rigorous evaluation comparing high-quality surveillance data and simulation studies, the MSP tool will be used to generate annual estimates of global measles mortality as from 2008.

4.2.2 *Haemophilus influenzae* type b and pneumococcal disease

Credible estimates of the global and regional burden of *Streptococcus pneumoniae* (SP) and *Haemophilus influenzae* type b (Hib) are needed to understand the relative

impact of these diseases and the potential for their control through public health interventions such as vaccination. Such estimates are also important for economic analyses and to advocate for national and international investment in SP and Hib control.

The WHO Hib and SP Global Disease Burden project estimated cases and deaths (and those averted by vaccination) from Hib and SP among children under five years of age at the national, regional, and global levels during the period 2000–2006. The approach was to estimate Hib and SP meningitis, pneumonia and invasive non-pneumonia/non-meningitis cases and deaths separately. The project was a collaborative effort between IVR, the EPI+ team, GAVI's PneumoADIP based at Johns Hopkins University, and GAVI's Hib Initiative based at the London School of Hygiene and Tropical Medicine. More than 70 investigators were involved in the study, which took place from 2004–2007. Results will be published in early 2008.

An exhaustive literature review, data abstraction, and data quality assessment were conducted for published reports of invasive Hib and SP disease. Over 400 of the 13 000 citations reviewed were included in the analysis dataset for meningitis and non-pneumonia/non-meningitis. Country-level Hib and SP meningitis and non-pneumonia/non-meningitis estimates were generated using meta-analyses of the data from the literature to obtain incidence and case-fatality rates, the latter adjusted for country-specific access to care. For countries where no data were available, a hierarchical imputation approach was used – combining data from neighbouring countries with similar under-5 mortality rates – to obtain estimates. The pneumonia case and death estimates were generated using the vaccine efficacy estimates for different clinical end-points from large Phase III efficacy studies of Hib and SP vaccine as proxies for the proportion of deaths from acute respiratory infections and cases due to these organisms. All estimates were adjusted for HIV seroprevalence and Hib vaccine use. National estimates were sent to countries for review in advance of publication, and to acquire any "grey literature" data available.

The disease burden estimates are expected to assist countries in their policy deliberations regarding Hib and pneumococcal conjugate vaccine introduction. These estimates are particularly timely in the light of innovative financing mechanisms for developing countries to accelerate vaccine introduction through the GAVI Alliance. Two such tools are the recently launched Advanced Market Commitment (see Section 2.3.2), representing a pledge of US$ 1.5 billion for the purchase of new pneumococcal vaccines for GAVI-eligible countries; and the International Finance Facility for Immunisation, a US$ 4 billion international development financing mechanism designed to accelerate the availability of funds for health and immunization programmes.

4.2.3 Rotavirus mortality data

IVR participated in an analysis which led to the development and publication in 2006 of official WHO figures for rotavirus-associated mortality.[5] An estimated 527 000 infants and young children died in 2004 due to rotavirus, 85% of whom lived in Africa and Asia. Interestingly, the report also highlighted that, although the absolute numbers of rotavirus-associated deaths are higher in Asia, the rates of death per 100 000 population are in fact substantially higher in Africa (Fig. 4).

FIG. 4. ROTAVIRUS DEATHS UNDER FIVE YEARS OF AGE PER 100 000, 2004

N.B. Globally these 527 000 child rotavirus deaths accounted for approximately 5% of all child deaths and the cause-specific mortality rate was 86. National cause-specific mortality rates ranged from 439 (Sierra Leone) to less than 1 (50 countries). The above seven countries had an under five rotavirus mortality rate of greater than 300.

Data source: WHO Department of Immunization and Biologicals, 2004. www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/index.html.

4.3 Health economic research

Economic and financial information on the optimal use of vaccines are important components of the evidence needed by countries and the international community to be able to set priorities. IVR carries out health economics-related implementation research to bridge the evidence gap between product development and the programmatic use of vaccines. Typically, this involves costing and cost-effectiveness studies, cost of illness and willingness to pay studies, as well as innovative financing mechanisms for the optimal use and scaling up of vaccines.

Economic research on health inherently intersects with various areas of operational research, such as studies on the optimal use of vaccines and innovative immunization delivery systems. Illustrations of IVR's health economic research at national and global level are provided below.

4.3.1 Future HIV vaccine delivery, access and cost-effectiveness project

To avoid delayed and ineffective access to future HIV vaccines, IVR supported a study to assess national preferences and expectations for future HIV vaccines, and to estimate the cost-effectiveness of HIV vaccination programmes in different country and epidemiological settings.

IVR is involved in the ongoing WHO–UNAIDS Collaborative Study on Cost-effectiveness, Delivery and Future Access to HIV Vaccines, which includes ministries of health and academicians from five countries (Brazil, China, Kenya, Peru and Thailand) and partners such as the US Wayne State University, the International AIDS Vaccine Initiative and the Futures Institute.

The study used a key informants questionnaire to elicit from the study countries their current vaccine delivery capacity and the profile they would find acceptable for potential HIV vaccines. During 2006–2007, an inter-country analysis of the questionnaire was performed, from which it became evident that a country's rating of the importance of vaccine effectiveness on susceptibility, infection and progression of HIV/AIDS, and how their associated minimum values for effectiveness relate, were not necessarily consistent with vaccine theory. These preliminary findings were presented at different scientific events, such as the AAVP Forum (Yaounde, 2006) and the International Health Economics Association Conference (Copenhagen, 2007). It remains a challenge to collect reliable and useful information on hypothetical interventions, i.e. HIV vaccine characteristics and health systems delivery strategies.

A mathematical modelling exercise called *HIV VaccSim* was also undertaken to estimate the population level impact and relative cost-effectiveness of potential HIV vaccination strategies under various scenarios. The model was demonstrated and, along with a user manual, used as a training tool at various workshops and conferences, e.g. at the International AIDS Conference in Toronto in 2006. In addition, validation exercises are ongoing to adapt the generic *HIV VaccSim* model to country-specific circumstances, e.g. during a concentrated versus a generalized HIV epidemic. The country-specific models will provide decision-makers with modelling data on vaccination policy considerations to assist in developing national capacity for future HIV vaccine adoption and effective delivery systems. Furthermore, *HIV VaccSim* will provide information to delineate the long-term financial requirements for sustainable HIV vaccination programmes. In this context, national (Bangkok, July 2006) and international training workshops (Bangkok, February 2006 and Beijing, September 2006) were held to demonstrate to public health experts how to use the tool for policy- and decision-making.

The general conclusion of the research showed that the epidemic could be controlled with moderately effective vaccine, and that such an intervention could be cost-effective. The final results of this collaborative study are expected in 2008, including country-specific cost-effectiveness information on HIV vaccine delivery strategies.

4.3.2. Socioeconomic behavioural studies on oral cholera vaccine in endemic situations

Once a vaccine has been registered, studies are needed in different parts of the world, and in populations with different age, gender and ethnic make-up, to overcome obstacles, and to monitor and improve the vaccine in use. An example of IVR's involvement in this type of implementation research is the "Pre-emptive use of a cholera vaccine in vulnerable populations at risk" study (Section 2.5.7).

The overall goal of the project, to be conducted over the 2007–2009 period, is to determine the potential utilization and mechanism of pre-emptive delivery of cholera vaccine to prevent outbreaks in endemic regions. An essential component of the study is the evaluation of the feasibility of a "revolving" stock of vaccine and of the financial sustainability of maintaining this revolving stock. Documentation and interviews with WHO experts on the working mechanism of a stockpile of meningitis and yellow fever vaccine – the most likely model to adopt – were collected. In particular, lessons learnt from the functioning of the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control and its applicability for oral cholera vaccines will be further reviewed.

4.3.3 Cost estimation of rotavirus disease and cost-effectiveness of rotavirus vaccines

Following a recommendation of the Advisory Committee on Diarrhoeal and Enteric Disease Vaccines, a meeting on this topic was organized in March 2006. The outcomes of the meeting contributed to the finalization of a cost-effectiveness model for rotavirus vaccines, which was included in the development of the GAVI Investment Case (an essential document reviewed by the GAVI Alliance Board prior to a decision on investment in a particular vaccine), and incorporated into the WHO Guidelines for the Standardization of Economic Evaluations in the Field of Vaccine-Preventable Diseases. The model also served as the basis for two satellite symposia with developing country researchers on rotavirus vaccines, i.e. the "Vaccine Financing Workshop" at the 8th Commonwealth Congress on Diarrhoea and Malnutrition (Dhaka, February 2006) and "Health Economics and their Impact on Enteric Vaccines" at the 4th International Conference on Vaccines Against Enteric Diseases (Lisbon, April 2007). The outcomes were also reported in the *Weekly Epidemiological Record*.[6]

4.3.4 Global Immunization Vision and Strategy costing tool

IVR is committed to all goals of the Global Immunization Vision and Strategy (GIVS),[1] and clearly has an important role to play to "Strengthen country capacity to determine and set policies and priorities for new vaccines and technologies" (Strategic Area II, Strategy 8). In particular, this role involves strengthening country capacity to assess disease burden and the cost and cost-effectiveness of new vaccines and technologies through the use of standards.

The GIVS costing tool, developed by IVR in collaboration with UNICEF, is an approach to estimate the cost of scaling up immunization activities. The tool is used to generate burden of disease, costing, and financing data that can help estimate the cost

and impact of the GIVS in the 117 countries defined as low- and lower middle-income in 2005. A manuscript describing the methodology and results was published in the *Bulletin of the World Health Organization* in 2007,[6] and serves as an important resource for understanding global costs and future cost-effectiveness analyses.

The GIVS costing tool will also be useful for diverse purposes such as building GAVI Investment Cases, evaluating the cost-effectiveness of new vaccines for priority setting, and for periodic updating of the estimates of immunization costs.

4.4 Operational research: revisiting immunization schedules

Optimizing the use of existing health interventions, or planning the appropriate use of future interventions, requires operational research. Activities under this umbrella cover a broad spectrum of quantitative and computational work, as well as some qualitative research. IVR focuses on the following areas of strategic importance in line with the normative functions of WHO.

Today's basic immunization schedules were initially developed according to age-specific disease incidence, operational considerations and the immunity elicited by the vaccine. Schedules have in the meantime been adapted to regional strategies and country needs. In addition, vaccine may not always be delivered according to the recommended schedule, and delays in immunization are common. The basic immunization schedules have frequently been taken as a reference point for the inclusion of new vaccines, in order to keep immunization contacts simple and allow for combination vaccines based on DTP. Hence, schedules have not been optimized for a number of newer vaccines, in particular the conjugated vaccines containing bacterial capsular polysaccharides. These vaccines not only provide individual protection, but may confer herd immunity by impeding colonization by, and therefore the transmission of pathogens. In the past biennium, IVR initiated several studies to examine systematically the evidence base for improved vaccination schedules.[7]

4.4.1 Reviewing the actual age of vaccination

To understand better the reality of today's vaccine delivery according to EPI schedules, IVR commissioned in 2006 a study with the London School of Hygiene and Tropical Medicine to review the actual age of immunization based on demographic health survey data from 55 countries. A major finding was a progressive delay in the administration of DTP vaccines, moving from a median delay of 1.2 months for DTP1 to 2.2 months for DTP3. While delays appear more common in rural areas, patterns vary from country to country, reflecting different immunization practices. The results of the study will be published in early 2008.

4.4.2 Reviewing immunization schedules of conjugated vaccines

Schedules that optimize the public health impact of conjugated vaccines are yet to be defined, be it in relation to primary immunizations, booster requirements or catch-up

strategies. For all three groups of conjugated vaccines (Hib, pneumococcal and meningococcal vaccines) the indirect effects related to the vaccines' capacity to reduce nasopharyngeal carriage have been demonstrated. The University of Bristol, under contract with IVR, has conducted a thorough review of experience and knowledge on the use of conjugated vaccines, with specific emphasis on indirect vaccine effects. While this work is being published, IVR is developing a research agenda to build the evidence for improved immunization schedules.

Implementation Research References

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5 Summary of IVR progress over 2006–2007 and projections for 2008–2009

5.1 Reaching the targets for 2007

WHO is moving increasingly towards longer-term strategic planning and objectives. The IVR Strategic Plan 2006–2009 described in detail the focus and planned activities over that four-year period, and set indicators and targets to monitor its progress. Section 5.1 shows the mid-term achievements of IVR towards these targets. While this work will continue in the next biennium, Section 5.2 presents how IVR is integrated in the new six-year WHO Medium-term strategic plan 2008–2013,[1] and the milestones it has set in that context.

EXPECTED RESULT 1

Knowledge managed, guidance provided and partnerships established for the development and early introduction of new vaccines and technologies

Indicator	Status Jan 2006	Target for end 2007	Status
Number of disease-specific research agendas established for four priority diseases through broad consultation with developing countries and research partners, and endorsed by the IVR Vaccine Advisory Committee.	0 of 4	2 of 4	3 of 4

Activities on course

- ✓ Dengue and enterotoxigenic *E. coli* clinical guidelines developed.
- ✓ Diarrhoeal diseases: white paper on product development and criteria for selection of enterotoxigenic *E. coli* vaccine candidates published.
- ✓ Flaviviruses: action plan for definition of correlates of protection for dengue vaccines established; partnership agreement with the Pediatric Dengue Vaccine Initiative signed.
- ✓ Human papillomavirus: Organization-wide workplan on HPV vaccine introduction developed.
- ✓ Pandemic influenza: global action plan on vaccine supply established; funding for technology transfer projects secured.
- ✓ Jet injectors: consensus on regulatory pathways for immunization established.
- ✓ Malaria: vaccine technology roadmap launched at the 2006 Global Forum for Health Research.

- ✓ Meningitis: strategic research plan for carriage studies in Africa submitted for funding.
- ✓ Rotavirus: recommendations on upstream vaccine R&D prompted new funding initiative.
- ✓ Rotavirus and pneumococcus: GAVI Investment Cases approved by GAVI Board.

Impediments

↓ Limited human and financial resources.

EXPECTED RESULT 2

Research promoted and supported, and capacity strengthened for the development and evaluation of WHO priority new vaccines and technologies

Indicator	Status Jan 2006	Target for end 2007	Status
Number of new vaccines against Japanese encephalitis, meningococcal A and measles that have entered Phase II/III clinical trials in developing countries.	0 of 3	2 of 3	2 of 3
Capacity to conduct vaccine clinical trials that meet international standards established in Ethiopia, India, Kenya, Mali, Mexico and the United Republic of Tanzania	1 of 6	5 of 6	5 of 6

Activities on course

- ✓ HIV: three technical guidance documents published on ethics and regulatory vaccine research.
- ✓ HIV: the African AIDS Vaccine Programme launched a new strategic plan and selected three centres of excellence in Africa to implement its workplan.
- ✓ Pandemic influenza: six developing country manufacturers had technology transferred and capacity strengthened for the production of influenza vaccines.
- ✓ Japanese encephalitis: two vaccines entered paediatric development in developing countries, with technical advice from IVR.
- ✓ Malaria: completion of Phase I trial in China of a vaccine candidate, with WHO support in GCP training and ethical review.
- ✓ Measles: capacity strengthened in India and Mexico for measles aerosol project.

✓ Meningitis: Phase II trial of conjugate meningitis A completed (the Gambia and Mali); and capacity strengthening activities conducted in Ethiopia, the Gambia, Ghana, Mali and Senegal.

Impediments

↓ Reprioritization of measles aerosol activities led to cancellation of Mexico trial.

↓ Pivotal Phase II trial of measles aerosol project reprogrammed to 2008 in India.

EXPECTED RESULT 3

Tools developed to measure disease burden and assess cost-effectiveness for new vaccines and technologies or to optimize the use of existing vaccines

Indicator	Status Jan 2006	Target for end 2007	Status
Number of new vaccines (particularly pneumococcal, meningococcal A, Japanese encephalitis, rotavirus, human papillomavirus) for which evidence has been generated on the appropriateness for introduction into immunization programmes.	0 of 5	2 of 5	2 of 5
Number of countries where pilot testing of a tool to estimate cost-effectiveness of future introduction of HIV vaccines completed (Brazil, China, Kenya, Peru, Thailand)	2 of 5	5 of 5	5 of 5

Activities on course

✓ HIV vaccines: tool to estimate cost-effectiveness of delivery strategies of future HIV vaccines developed and pilot tested in all target countries. Application to other countries (e.g. South Africa) under discussion.

✓ Japanese encephalitis: together with WHO regions, guidelines for vaccine introduction and methods for laboratory diagnosis developed.

✓ Pneumococcus and *Haemophilus influenzae* type b: disease burden data modeled and ready for approval. Detailed documentation led to SAGE recommendation on the use of PCV7. Pneumococcal target product profile for Advanced Market Commitment communicated to the GAVI Alliance by WHO Director-General.

✓ Rotavirus and human papillomavirus: cost-effectiveness models developed and scheduled for country validation. Extensive evidence on HPV accumulated and published. SAGE recommendation expected 2008.

5.2 Longer-term results-based management

Impediments

None.

Today, it is widely acknowledged that health objectives require a significantly longer period than the traditional biennial reporting system to achieve tangible results. A vaccine, for example, can take at least 10 years from identifying an immune response to introducing an effective vaccine into the market. As from 2008, six-year medium-term strategic plans will form the framework for WHO's results-based management, within which the global health agenda will be addressed. The WHO Medium-term strategic plan 2008–2013 sets out 13 complementary strategic objectives, each of which has a series of expected results for which the Secretariat is accountable, along with indicators, targets and the resources required for its achievement.

One of the priorities of the WHO Eleventh General Programme of Work[2] is to address the global burden of communicable diseases, and this is reflected in several WHO strategies aimed at reducing the burden of HIV, tuberculosis, malaria and vaccine-preventable diseases. From 2008, IVR will be specifically accountable to these strategies as follows:

Strategic Objective 1: Reduce the health, social and economic burden of communicable diseases.

Global scope: Work that focuses on prevention, early detection, diagnosis, treatment, control, elimination and eradication measures to combat communicable diseases that disproportionately affect poor and marginalized populations. The targeted diseases include, but are not limited to: vaccine-preventable, tropical, zoonotic and epidemic-prone diseases, excluding HIV/AIDS, tuberculosis and malaria.

Expected result: New vaccines, related technologies and implementation strategies that meet priority needs for the prevention of communicable diseases developed and validated.

Indicator	Target for end 2009
Number of consensus reports published on global research needs and priorities for vaccines or immunization technologies or strategies.	1
Number of new or improved tools (vaccines and immunization	1

technologies) and implementation strategies developed with significant WHO contribution which have been translated into public sector policy and use in at least one developing country.

Strategic Objective 2: Combat HIV/AIDS, tuberculosis and malaria.

Global scope: Work will focus on: scaling up and improving prevention, treatment, care and support interventions for HIV/AIDS, tuberculosis and malaria so as to achieve universal access, in particular for seriously affected populations and vulnerable groups; advancing related research; removing obstacles that block access to interventions and impediments to their use and quality; and contributing to the broader strengthening of health systems.

Expected result: New knowledge, vaccines and related technologies, as well as implementation strategies that meet priority needs for vaccination against HIV/AIDS, tuberculosis and malaria developed and validated.

Indicator	Target for end 2009
Number of consensus reports published on global research needs and priorities and current status in relation to HIV, tuberculosis or malaria vaccines and immunization strategies	1
Number of clinical trial end-points and/or assays developed and validated for clinical evaluation of vaccines for HIV, tuberculosis and malaria	3

Summary References

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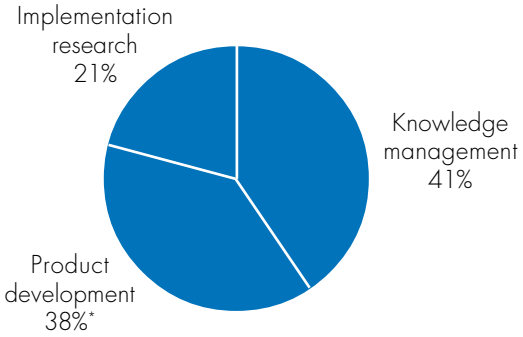
Annex 1. IVR resources

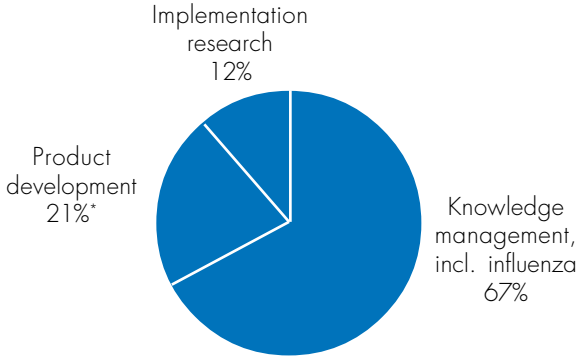
Total IVR/HQ expenditure in 2006–2007 was US$ 28 013 000, which includes staff, administrative and operating costs, but not monies disbursed through WHO regional offices. It also includes US$ 12 500 000 disbursed on technology transfer grants to developing countries to increase their influenza vaccine production capacity. A breakdown of the total expenditure by type of research carried out by IVR is as follows.

IVR EXPENDITURE BY TYPE OF RESEARCH (EXCLUDING INFLUENZA TECHNOLOGY TRANSFER GRANTS)



* includes significant clinical trial costs of the measles aerosol vaccine

IVR EXPENDITURE BY TYPE OF RESEARCH (INCLUDING INFLUENZA TECHNOLOGY TRANSFER GRANTS)



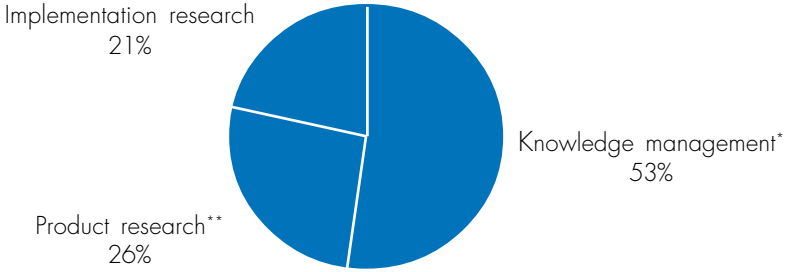
* includes significant clinical trial costs of the measles aerosol vaccine

Annex 2. IVR database of vaccine research activities

The IVR database of vaccine research and development activities was created in 2004 to allow a more detailed picture of how IVR resources contribute to global vaccine research priorities. The database comprises primarily research grants, contracts to external scientists and collaborators, IVR-sponsored meetings, and the publication and dissemination of vaccine R&D materials. It does not include staff costs or travel, or any operating expenses.

In addition to a disease focus, the database provides information on equally important aspects such as capacity strengthening of investigators and institutions in developing countries, scientific advances in the development of new technologies for vaccine formulation and delivery, and the provision of tools for evidence-based decision-making. Such a categorization will also be useful in the context of WHO's current efforts to identify and streamline its role in health research.

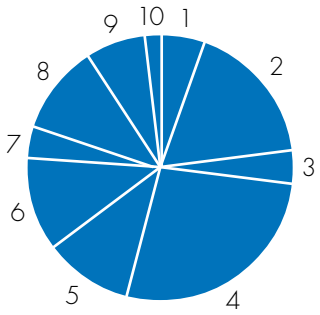
IVR VACCINE R&D ACTIVITIES BY TYPE OF RESEARCH, AS A PERCENTAGE OF TOTAL PROJECT EXPENDITURE



* excludes grants to facilitate influenza vaccine production capacity in developing countries (US$12 500 000)

** includes the measles aerosol clinical trial costs (US$500 000).

IVR VACCINE R&D BY DISEASE, AS A PERCENTAGE OF TOTAL PROJECT EXPENDITURE



1	All (> 3 diseases)[a]	5,5%
2	Diarrhoeal diseases	17,4%
3	Flaviviruses	4,1%
4	HIV	27,2%
5	HPV	10,3%
6	Influenza[b]	11,6%
7	Malaria	4,1%
8	Measles aerosol[c]	11,2%
9	Men, pneumo, Hib[d]	7%
10	Other (rabies, Leish, TB)	1,7%

[a] projects that cover more than three diseases

[b] excludes grants for developing countries to increase influenza vaccine production capacity

[c] includes clinical trial costs as well as cross-cutting measles implementation research

[d] combines activities related to the Meningitis Vaccine Project, and research on meningococcal, pneumococcal and Hib infections

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* These and other new positions, such as for vaccine introduction, are under consideration.

Annex 5. IVR advisory groups

Theme/Committee	Participants	Scope of advice
IVR Advisory Committee	Global partners in vaccine R&D	Strategy direction, cross-disease synergies
HIV	WHO, UNAIDS and scientific experts and stakeholders	Policy and ethics; access to future vaccines
Malaria	Scientific experts and key partners	International collaboration, evaluation of new vaccines, neglected lines of research
Dengue and other flaviviruses	Scientific experts	Development and evaluation of new flavivirus vaccines and technical advice in relation to the yellow fever vaccine
Diarrhoeal/enteric diseases	Scientific experts and key partners	International collaboration, monitoring scientific and technical progress
Human papillomavirus	Scientific experts and stakeholders	International coordination, programmatic options, synthesis of evidence on cervical cancer and related diseases
Pandemic influenza	Country representatives and donors/partners	Evaluation and implementation of short- to medium-term options to develop sufficient pandemic vaccine to immunize the world's citizens
Measles Product Development Group	Scientific experts, product developers and regulators	Technical guidance for the development of the measles aerosol vaccine
Quantitative Immunization and Vaccines Research	Scientific experts	Burden of disease estimation, modelling of vaccine interventions, economic evaluations, analysis of operational and implementation research

Annex 6. IVR collaboration with Product Development Partnerships or Programmes

Partnership	Programme
European Commission and interested European Union Member States	European Malaria Vaccine Initiative
The GAVI Alliance	PneumoADIP based at Johns Hopkins Bloomberg School of Public Health, USA
	Rotavirus Vaccine Program (rotavirus ADIP) based at PATH
International AIDS Vaccine Initiative	
International Vaccine Institute	Pediatric Dengue Vaccine Initiative
PATH	Enteric Vaccine Initiative
	Vaccine Research Program for Pandemic Influenza
	Japanese Encephalitis Project
	Malaria Vaccine Initiative
	Meningitis Vaccine Project

IVR's vision

is a world in which optimal vaccines and technologies are developed and effectively used to protect all people at risk against infectious diseases of public health importance, especially in developing countries.

www.who.int/vaccine_research

We see impressive progress in the introduction of new and underutilized vaccines, with even more new vaccines expected within the next 10 years.

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World Health Organization

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