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THE INITIATIVE FOR VACCINE RESEARCH

Strategic plan 2006–2009

World Health Organization

WHO/IVB/06.08

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thanks the donors whose unspecified financial support has made the production of this publication possible.

Grateful acknowledgement is also extended to Irina Serdobova for her expert advice on core strategic issues, to Kay Bond for her editorial support, and to all others involved in its development under the leadership of Director IVR.

This publication is available on the Internet at www.who.int/vaccine_research/documents/en/

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Ordering code: WHO/IVB/06.08

Cover photo: WHO/TDR/Crump

Design and layout: Alessandra Bonrruquer

Printed in India.

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IVR STRATEGIC PARTNERS, AND SPONSORS OF VACCINE RESEARCH

AAVP	African AIDS Vaccine Programme
ADIP	Accelerated Development and Introduction Plan
Aeras	Aeras Global Tuberculosis Vaccine Foundation (USA)
ANRS	Agence Nationale de Recherches sur le SIDA (France)
ARC	American Red Cross (USA)
BMGF	The Bill and Melinda Gates Foundation
CDC	Centers for Disease Control and Prevention (USA)
CIDA	Canadian International Development Agency (Canada)
CVD	Center for Vaccine Development (USA)
CVP	Children's Vaccine Program at PATH (USA)
DFID	Department for International Development (UK)
EDCTP	European and Developing Countries Clinical Trials Partnership
EMVI	European Malaria Vaccine Initiative
EU	European Union
GAVI	Global Alliance for Vaccines and Immunization
GBUI	Global Buruli Ulcer Initiative
GHVE	Global HIV Vaccine Enterprise
HVI	Joint WHO-UNAIDS HIV Vaccine Initiative
IARC	International Agency for Research on Cancer
IAVI	International AIDS Vaccine Initiative
IDRI	Infectious Disease Research Institute (USA)
IVB	WHO Department of Immunization, Vaccines and Biologicals
IVI	International Vaccine Institute (Republic of Korea)
IVR	WHO Initiative for Vaccine Research
LSHTM	London School of Hygiene and Tropical Medicine (UK)
MCRI	Murdoch Children's Research Institute
MRC	Medical Research Council (UK)
MVI	Malaria Vaccine Initiative at PATH (USA)
MVP	WHO-PATH Meningitis Vaccine Project
NCI	National Cancer Institute (USA)
NHMRC	National Health and Medical Research Council (Australia)
NIAID	National Institute of Allergy and Infectious Disease (USA)
NIH	National Institutes of Health (USA)
PAHO	Pan American Health Organization/World Health Organization Regional Office for the Americas
PATH	Program for Appropriate Technology in Health
PDVI	Pediatric Dengue Vaccine Initiative at IVI (Republic of Korea)
RAPID	Rotavirus Action Partnership for Immunization and Development
RBM	Roll Back Malaria
SIDA	Swedish International Development Cooperation Agency (Sweden)
TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
UNDP	United Nations Development Programme
USAID	United States Agency for International Development (USA)
USDA	United States Department of Agriculture (USA)
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research (USA)

EXECUTIVE SUMMARY

Vaccines protect millions of lives worldwide against infectious disease. In spite of this success, close to 6.7 million children under five years of age still die each year from infections.[1] Part of this death toll could be prevented through better use of existing vaccines, whereas targeted research and product development are needed for new or improved vaccines against diseases that are currently not preventable through immunization, or for which existing vaccines are of suboptimal efficacy.

Emphasizing this, the World Health Assembly in 2005 urged Member States to adopt an ambitious and comprehensive Global Immunization Vision and Strategy (GIVS) for 2006–2015 to fight communicable diseases[2]. GIVS has three main aims:

1. to immunize more people against more diseases;
2. to introduce a range of new vaccines and technologies; and
3. to take advantage of immunization contacts to deliver other critical health interventions.

The process of developing vaccines is complex, risky and lengthy: it usually takes more than 10 years to arrive at a fully licensed product. Moreover, the required investment both of capital and highly skilled expertise is substantial and, as a result, those who most need the vaccines are the least able to afford or develop them. Commercial realities also push most vaccine research and development (R&D) efforts towards products for infectious diseases that affect the industrialized world, leaving little investment for the development of preventive tools for diseases that predominantly touch poor and neglected populations.

Even when an efficient vaccine is developed and licensed, R&D should not stop there. Implementation research — e.g. post-marketing surveillance, bridging studies that enable expansion of immunization strategies into still larger populations, and impact evaluation — is a vital component of successful vaccine introduction.

The establishment of the Initiative for Vaccine Research (IVR) is WHO's response to these challenges. IVR is an international team of scientists, managers, and technical experts whose task is to facilitate the development of vaccines against infectious diseases of major public health importance, to improve existing immunization technologies, and to ensure that these advances are made available to the people who need them the most. IVR will achieve these objectives using a three-pronged approach:

1. Management of knowledge and provision of guidance and advocacy through effective partnerships to accelerate innovation for new and improved vaccines and technologies;

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[1] Epidemiological data in this publication are taken from *The world health report 2004: changing history* (Geneva, World Health Organization, 2004) and *The world health report 2005: make every mother and child count, Annex Table 3* (Geneva, World Health Organization, 2005).

[2] *Global Immunization Vision and Strategy 2006–2015*. Geneva, World Health Organization and UNICEF, 2005 (WHO/IVB/05.05).

2. Support to research and product development for WHO priority new vaccines and technologies;

3. Conduct of appropriate implementation research, and development of tools to support evidence-based recommendations, policies and strategies for optimal use of vaccines and technologies.

IVR is administratively hosted within the WHO Department of Immunization, Vaccines and Biologicals and works in close collaboration with a wide range of units within the Organization. Its two major constituencies are the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the Joint United Nations Programme on HIV/AIDS (UNAIDS). IVR also acts as focal point within WHO for interaction on vaccine R&D with external partners and organizations which collectively play a vital part in enriching the global vaccine pipeline.

This IVR Strategy 2006–2009 is an integral part of the Strategic Plan 2006–2009 of the Department of Immunization, Vaccines and Biologicals (IVB), as well as other major WHO policy documents.

1. INTRODUCTION

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.

1.1 THE NEED FOR INCREASED INVESTMENT IN VACCINE RESEARCH

Vaccines are the cornerstone of the fight against communicable diseases, as demonstrated by the success of smallpox eradication, the dramatic reduction in polio cases and deaths due to measles, and progress towards tetanus elimination. In spite of this, infectious diseases are still responsible for close to 30% of all deaths worldwide, representing more than 15 million people – of whom some 6.7 million children – every year, mostly in low- and middle-income countries. Around 1.5 million of these deaths could be averted if available vaccines were universally applied. Most important, there are currently no licensed vaccines to combat some of the major child killer diseases.

Achievement of the United Nations Millennium Development Goals requires innovation and breakthroughs to accelerate vaccine R&D. The targets for 2015, such as reducing child mortality rates by two thirds (Goal 4), combating HIV/AIDS, malaria and other diseases (Goal 6), and forging global partnerships to ensure access to medicines (Goal 8), are highly pertinent to the whole vaccine community.[1] New and improved vaccines and better and equitable access to existing vaccines, will contribute substantially to the global efforts to achieve these goals and to reduce poverty worldwide.

Although the process for developing vaccines is lengthy, complex and expensive, there are reasons to be optimistic.

Firstly, a number of new vaccines have been developed and licensed by industry in recent years. Technological and scientific advances, hastened by the biotechnology revolution and a growing understanding of how vaccines induce immunity against diverse pathogens, have collectively shaped the rational development of vaccination strategies.

Secondly, since the mid 1990s, increased awareness of health issues in the developing world has led to the emergence of a variety of research-based, non-profit-making organizations and public–private partnerships. Four of these, that focus on R&D of vaccines against the major poverty-related killer diseases of AIDS, malaria and tuberculosis, are the International AIDS Vaccine Initiative, the Malaria Vaccine Initiative, the European Malaria Vaccine Initiative and the Aeras Global TB Vaccine Foundation. Vaccines against two of the most severe agents of child mortality – rotavirus and pneumococcus – have now been licensed, and targeted projects called Accelerated Development and Introduction Plans (ADIPs) will hasten access of

[1] See www.who.int/mdg/en/ for more information on WHO and the UN Millennium Development Goals.

developing countries to these potentially life-saving novel vaccines. IVR will further complement the ADIP work by taking a broader perspective on the rotavirus and pneumococcus vaccine research agenda, promoting support for the evaluation of early stage products, and investigating neonatal and alternative vaccination schedules. Other successful partnerships include the WHO-PATH Meningitis Vaccine Project, which is pioneering efforts to develop a low-cost conjugate *Neisseria meningitidis* serogroup A vaccine for Africa. The IVR-led Measles Aerosol Project is engaged in product R&D for a new aerosol formulation of a measles vaccine, which could increase vaccine coverage.

Yet a number of diseases still lack the strong leadership, partnerships, funding and supportive implementation research necessary to bring a vaccine to market. These include enteric diseases (e.g. shigellosis), tropical diseases (e.g. schistosomiasis and leishmaniasis), and various viral and bacterial respiratory infections. The threat of emerging pandemics such as Severe Acute Respiratory Syndrome (SARS) or influenza, and bioterrorism, are particularly dangerous for developing countries, where population density is high and medical treatment less efficient or lacking. The ability to scale up vaccine manufacturing capacity in response to epidemics, and improved disease surveillance, are other important challenges being faced today.

During 2006–2009, IVR will continue to encourage increased investment in vaccine research and contribute to the work of public–private partnerships by:

- engaging in product R&D in its area of comparative advantage;
- facilitating clinical and/or laboratory standards and protocols;
- strengthening developing country capacity in the areas of bioethics, regulation and Good Clinical Practice; and
- conducting implementation research, including that on future access (cost–effectiveness studies, introduction plans, national decision-making support tools).

1.2 THE GLOBAL VACCINE RESEARCH PIPELINE

The research and product development process bridges the gap between scientific discovery and the delivery of tools for health interventions. Vaccines used today are the yield of decades of devoted effort, requiring not only excellence in research, but also managerial and funding commitment throughout the endeavour. The total cost of the R&D process for a single vaccine candidate is estimated at US$200 million to US$500 million.[2] As stated earlier, vaccine R&D is also a high-risk undertaking. Viewed statistically, the probability for a preclinical vaccine candidate reaching the market has been estimated at 0.22, i.e. odds of around 5 to 1 for failure. As a result, registration of a single vaccine requires the development of four to five independent vaccine candidates[3] and a constant pipeline of potential new products. For a vaccine to ever emerge on the market, the pipeline must be composed of an R&D port-folio of different vaccine candidates in different stages of development for each target disease. Activities to accelerate the introduction of and access to future vaccines must also be planned.

Figure 1 provides the status of the global vaccine R&D portfolio pipeline as at September 2005, and the

[2] Andre FE. How the research-based industry approaches vaccine development and establishes priorities. *Journal of developmental biology*, 2002, 110:25–29.

[3] Struck MM. Vaccine R&D success rates and development times. *Nature Biotechnology*, 1996, 14: 591–593.

respective partners involved.[4] A number of gaps can be readily identified in this pipeline. For example, only one leishmaniasis vaccine candidate has entered clinical trials in the United States of America (USA) and Latin America. In the case of malaria, many vaccine candidates target the same parasite proteins, potentially duplicating efforts and overlooking novel target opportunities. For bacterial pneumonia, the current vaccines do not cover certain pathogen serotypes prevalent in developing countries and new vaccine candidates would need substantial investment to reach the market. For human papilloma virus and cervical cancer, a vaccine is planned for licensing in 2006 before sufficient information on its acceptability is available to ensure its effective introduction in populations who would benefit the most, such as adolescent girls in low-income countries.

Once an efficient vaccine is developed and licensed, certain information is still needed, notably on the public health impact and cost–effectiveness of the vaccine in different target populations. Implementation research addresses this through bridging studies and other post-regulatory approval activities, in order to ensure the broadest use of new vaccines and consequently to save more lives. Yet the pipeline should not stop there. Using the life-cycle approach applied to commercial vaccines, innovation and research into even better vaccines and vaccine delivery systems continue, for example towards improved manufacturing processes to reduce gradually the cost of a vaccine for the end user. The existence of an "evergreen" vaccine pipeline that constantly delivers new or improved products to the market is thus key.

[4] See www.who.int/vaccine_research/documents/en/Status_Table.pdf for a detailed review of the latest status of the vaccine development field for WHO research priority diseases.

Most candidate vaccines will require early stage analysis and planning to ensure adequate manufacturing capacity of quality vaccine and effective introduction. In addition, the global pipeline cannot operate efficiently and keep delivering optimal vaccines for resource-poor countries without the coordinated efforts of all partners to strengthen research and product development, regulatory and ethical review and post-marketing surveillance capacity in these countries. Most important, the participation of developing countries in setting and carrying out research priorities, and in defining target product profiles for new vaccines, is critical for the success of vaccine development and implementation.

In summary, despite positive trends, the current level of investment into building sustainable driving forces for vaccine research remains inadequate, and the complex global vaccine R&D pipeline suffers from significant gaps that reduce the chances of some essential vaccines being delivered.

A number of supporting mechanisms can be put in place by IVR on a case-by-case basis to harmonize the global research agenda and to facilitate product development, such as:

- proactively identifying and bridging research knowledge gaps;
- discovering, assessing and standardizing animal models and associated in vitro assays to facilitate preclinical vaccine evaluation;
- validating and standardizing clinical evaluation end-points and target product profiles;
- participating in the harmonization of internationally accepted standards and regulatory requirements for vaccine R&D (in collaboration with other dedicated WHO units);
- strengthening clinical trial sites for vaccine evaluation in developing countries;

FIG. 1 GLOBAL VACCINE R&D PIPELINE BY DISEASE OR INFECTIOUS AGENT OF PUBLIC HEALTH IMPORTANCE IN THE DEVELOPING WORLD: SPONSOR AND STAGE OF DEVELOPMENT

CATEGORY	DISEASE OR PATHOGEN	SPONSOR[b]	STAGE OF RESEARCH INTO MOST ADVANCED VACCINE CANDIDATE[a]
			Discovery / Preclinical / Clinical/regulatory / Post-registration / Introduction
Major poverty-associated infectious diseases	HIV	ANRS, BMGF, CDC, GHVE, IAVI, MRC, NIH, private sector	→ ♦
	Malaria	BMGF, EMVI, EU, MVI, NIH, USAID, private sector	→ ♦
	Tuberculosis	Aeras, BMGF, EU, NIH, private sector	→ ♦
Acute respiratory infections	Influenza (broad spectrum)	EU, NIH, private sector	→
	Pneumococcus	BMGF, CDC, CVP, EU, Johns Hopkins pneumoADIP, MRC, NIH, PATH, USAID, private sector	→ ♦
Diarrhoeal diseases	Cholera	BMGF, IVI, NIH, private sector	→ ♦
	Enterotoxigenic *Escherichia coli*	CVD, private sector	→
	Rotavirus	BMGF, CDC, PAHO, PATH rota ADIP, RAPID, USAID, private sector	→ ♦
	Shigellosis	CVD, IVI, NIH, WRAIR, private sector	→
	Typhoid	IVI, NIH, private sector	→
Flaviviruses	*Caliciviruses*	CDC, CVD	→
	Dengue	BMGF, PDVI, WRAIR, private sector	→ ♦
	Japanese encephalitis	BMGF, PATH, WRAIR, private sector	→ ♦

CATEGORY	DISEASE OR PATHOGEN	SPONSOR[b]	STAGE OF RESEARCH INTO MOST ADVANCED VACCINE CANDIDATE[a]
			Discovery / Preclinical / Clinical/ regulatory / Post-registration / Introduction
Parasitic diseases	Hookworm	BMGF, Public sector	→
	Leishmaniasis	BMGF, IDRI, public sector	→
	Schistosomiasis	EU, NIH, USAID	→
Other bacterial diseases	Buruli ulcer	GBUI	→
	Leptospirosis	USDA, private sector	→
	Neisseria meningitidis A,C,W135,Y	BMGF, MVP, private sector	→ ♦
	Streptococcus group A	NHMRC, NIH, private sector	→
	Streptococcus group B	NIH, private sector	→
	Trachoma	Private sector	→
Other viral diseases	Herpes simplex virus 2	NIH, private sector	→
	Human papilloma virus	BMGF, NCI, private sector	→
	Measles (aerosol)	ARC,BMGF, CDC, IVR, private sector	→

[a] The arrow indicates the stage of the most advanced vaccine candidate. A diamond, indicating that access research has started, should be present for all candidate vaccines before the post-registration stage. Fig. 1 highlights that this is not always the case.

[b] See list of abbreviations on page ii. This list is limited to international and national entities in industrialized countries supporting and leading global health research. Developing country institutions and private funded entities greatly contribute to this pipeline and are hereby acknowledged.

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

- strengthening national regulatory authorities in the area of clinical trial authorization and monitoring (in collaboration with other dedicated WHO units);
- supporting the development of National HIV Vaccine Plans;
- independent monitoring of vaccine clinical trials; and
- linking product development with implementation research early in the product development cycle.

IVR is committed to facilitate the development of high quality, safe, effective, affordable and accessible vaccines against infectious diseases of public health importance. The Initiative believes that all partners should work together to establish and promote a global, sustainable research and development pipeline delivering optimal vaccines and immunization technologies for priority infectious diseases. A new coordinated and converged vaccine R&D paradigm is required to meet the UN Millennium development Goals described above. Countries in the developing world should be instrumental in deciding which vaccines will be needed and how they should be administered; IVR will play its part in ensuring that this occurs.

1.3 DOCUMENT OUTLINE

The current document sets out to communicate IVR's vision, mission and areas of priority as an integral part of the IVB Strategic Plan 2006–2009, WHO's Medium-Term Strategic Plan 2008–2013 and the WHO 11th General Programme of Work 2006–2015. Having reviewed the need for increased investment in research and the gaps in the global vaccine R&D pipeline, IVR's mission and functions are outlined in response to these challenges. The guiding principles used by IVR to reach decisions on priority diseases, vaccines and technologies and the different types of IVR involvement are then described. Sections 3 and 4 illustrate the activities, milestones and indicators IVR has set itself to reach its global vaccine-related targets and expected results for the period 2006–2009. The planned expenditure of the Initiative for the next biennium is then provided by disease or technology, and the document closes with an extract from the WHO/UNICEF Global Immunization Vision and Strategy, underscoring the role that IVR will play to change the sobering fatality statistics provided above.

2. IVR MISSION AND STRUCTURE

IVR's mission is to accelerate innovation for the development and optimal use of safe and effective vaccines and technologies against infectious diseases of public health importance by providing vision, coordination, advocacy, guidance and support for research.

The Director-General of WHO launched the Initiative for Vaccine Research (IVR) in June 1999 at the Montreux Global Vaccine Research Forum. The rationale was to streamline the vaccine R&D endeavours of different areas of WHO, TDR and UNAIDS in order to maximize synergies and unify common goals. IVR's mandate is to provide leadership, vision, priority-setting and coordination of worldwide R&D efforts for the development of vaccines against neglected communicable diseases, particularly in developing countries where these diseases are endemic.

IVR unites individual vaccine research projects within the common research agenda of WHO's comprehensive health strategy. The vaccine research agenda draws on IVR's consultations with global public health research initiatives, donors, research institutions, policy-makers and countries. The Initiative is guided by the needs of WHO's 192 Member States and responds to the vaccine research priorities expressed by the World Health Assembly. An independent expert committee – the IVR Vaccine Advisory Committee – provides overall strategic and technical advice.

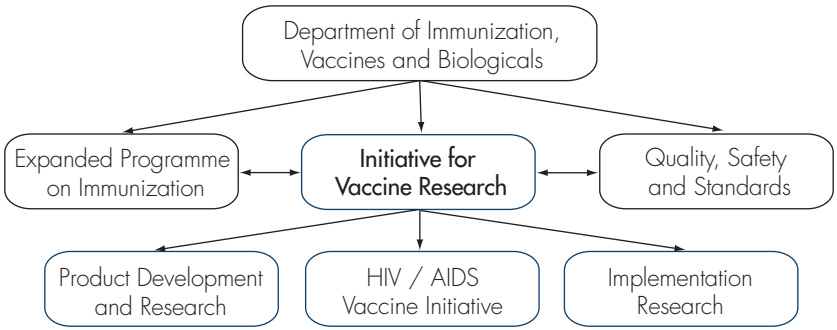
The Initiative is hosted by the WHO Department of Immunization, Vaccines and Biologicals (IVB) within the Family and Community Health cluster. Being part of IVB, IVR benefits from close proximity to teams involved in regulatory activities, norms and standards for production, quality control and safety of vaccines, implementation of immunization programmes, disease control, surveillance and epidemiology (Figure 2).

Within WHO, IVR works closely with other clusters such as Communicable Diseases; and HIV/AIDS, Tuberculosis and Malaria; as well as global initiatives such as Stop TB and Roll Back Malaria. In addition to IVB, IVR's two constituencies are TDR and UNAIDS. IVR also acts as focal point within WHO for interaction on vaccine R&D with external partners and organizations including the Global Alliance for Vaccines and Immunization (GAVI), the Program for Appropriate Technology in Health (PATH), the International Vaccine Institute (IVI), the International AIDS Vaccine Initiative (IAVI) and the Global HIV Vaccine Enterprise.

Finally, IVR takes into consideration the recommendations of three targeted advisory groups: the TDR Scientific and Technical Advisory Committee (STAC), the WHO-UNAIDS Vaccine Advisory Committee (VAC) and the WHO Strategic Advisory Group of Experts (SAGE). A number of specialized committees have also been set up to provide guidance on specific vaccines or technologies. Figure 3 illustrates diagrammatically how IVR benefits from its collaboration with these entities.

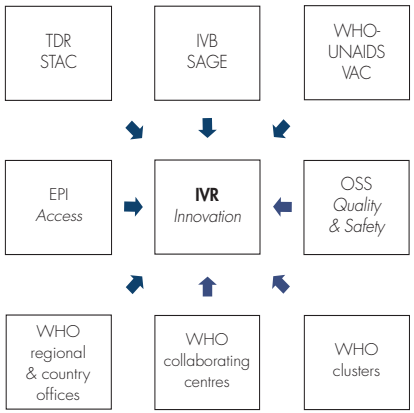
IVR has a particular responsibility to involve developing countries in research and decision-making. In this regard, IVR is committed to nurturing strong networks with

FIG. 2 IVR WITHIN THE WHO DEPARTMENT OF IMMUNIZATION, VACCINES AND BIOLOGICALS



developing country experts and research institutions, as well as with technical focal points in WHO regional and country offices. This approach will foster true collaborative work across the Organization and with Member States.

FIG. 3 SOURCES OF WHO INPUT TO IVR POLICIES AND ACTIVITIES



In its relatively short history as an Initiative, and with limited resources, research resulting from IVR's efforts has contributed to several notable achievements. Among these is the Gambian pneumococcal vaccine trial, sponsored by several partners including IVR, which showed that all-cause mortality was reduced by 16% in children vaccinated with an experimental 9-valent conjugate pneumococcal vaccine.[1] Another achievement has been the fostering of new investment into rotavirus vaccine development in response to the drawbacks of the first licensed ("Rotashield" Wyeth) vaccine, with the Secretariat of the global RAPID partnership hosted by

[1] Cutts FT et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in the Gambia: randomised, double-blind, placebo-controlled trial. *Lancet*, 2005 Apr;365(9465):1139–46.

BOX 1. EXAMPLE OF RESEARCH AND PRODUCT DEVELOPMENT: MEN A CONJUGATE VACCINE

Over 300 000 cases of cerebrospinal meningitis were reported between 1999 and 2004. The highest burden of disease occurs in sub-Saharan Africa within the 'meningitis belt', a savannah region that extends from Senegal to Ethiopia with an estimated population of 400 million. Despite treatment, at least 10% of patients die within days of onset and 10–20% of survivors develop significant neurological sequelae.

The goal of the Meningitis Vaccine Project, a 10-year partnership between WHO and PATH, is to eliminate epidemic meningitis as a public health problem in this area through the development, testing, introduction, and widespread use of conjugate meningococcal vaccines. The Project is currently pioneering the development of a low-cost conjugate *Neisseria meningitidis* serogroup A vaccine. Activities involve the coordination of clinical studies; consolidation of efforts to enhance surveillance and laboratory capacity in the meningitis belt; and support to core countries to validate their burden of disease and vaccination data in anticipation of the advent of conjugate vaccines.

Following the successful completion of the Phase I Men A conjugate vaccine trial in India among adult volunteers, Phase II trials are now under way to demonstrate safety, immunogenicity, and memory of the vaccine in the target population.

WHO. The IVR Report 2004–2005 provides further details of the achievements and challenges of the Initiative.[2]

IVR recognizes two, mutually reinforcing types of research, namely product development and implementation research, which are introduced here and described in further detail in Section 3.

2.1 RESEARCH AND PRODUCT DEVELOPMENT: THE RPD TEAM

In the past, this research has led to the development and evaluation of the immunogenicity of a slow release formulation for a tetanus vaccine, pioneering support for preclinical assessment of DNA vaccines and support to discovery research into chimeric *flavivirus* vaccines. Current product development targets include a meningitis vaccine for Africa and an aerosol formulation of a measles vaccine.

2.2 IMPLEMENTATION RESEARCH: THE IMR TEAM

Implementation research focuses on building the evidence base to support developing country decisions on vaccine introduction in their immunization programmes. For IVR, the term "implementation research" is used to encompass the following strategies:

- engage vaccine introduction and control programmes in discussions on optimal target product profiles for future vaccines and immunization technologies;
- assess disease burden, estimate and model vaccine impact, and determine cost–effectiveness;
- develop the necessary information and tools to facilitate national level decisions on prioritization, use and optimization of new or under-utilized vaccines and technologies;

[2] *The Initiative for Vaccine Research Report 2004–2005.* Geneva, World Health Organization, 2006 (WHO/IVB/06.05).

- undertake research aimed at increasing coverage using vaccines already included in national immunization programmes.

2.3 A WHO-UNAIDS JOINT VENTURE: THE HVI TEAM

The HIV Vaccine Initiative (HVI) is a joint WHO-UNAIDS programme. HIV vaccine activities were initiated in 1989 within the former WHO Global Programme on AIDS and have been hosted at the Initiative for Vaccine Research since 2001.

The mission of HVI is to promote the development, facilitate evaluation, and address future availability of preventive HIV vaccines, with a focus on the needs of developing countries.

With more than 15 000 new HIV infections occurring every day — 95% of them in developing countries — a safe, effective and widely available HIV vaccine is the best long-term hope for the control of the pandemic, in complement with other HIV prevention and treatment interventions. Since the first HIV candidate vaccine was clinically tested in 1987, more than 50 different candidates have been evaluated in Phase I/II trials. Three large-scale Phase III trials have been conducted thus far, including one in Thailand, which has received WHO support since 1991 for its National AIDS Vaccine Plan. The HVI team provides guidance and coordination to the international effort to develop and evaluate HIV vaccines. Although not directly involved in the development of candidate vaccines, HVI serves as an impartial broker between agencies, industry, host countries and communities, to ensure that vaccine research is conducted in accordance with the highest scientific and ethical standards, and that the needs of developing countries, which carry the largest burden of disease, are met.

HVI's strategy has four major components:

- advocating, guiding and coordinating the international HIV vaccine effort;
- promoting the development of appropriate vaccines for developing countries (conducted mostly through the WHO-UNAIDS Network for HIV Isolation and Characterization);
- facilitating the conduct of vaccine clinical trials in developing countries through training and capacity building; and
- working towards future access and availability of HIV vaccines.

HVI is guided by the WHO-UNAIDS HIV Advisory Committee, which provides a unique forum for coordination and exchange of information among the various stakeholders engaged in HIV vaccine research. The Committee also provides technical advice to WHO on various aspects of HIV vaccine development and clinical trials. HVI works in close collaboration with the WHO HIV/AIDS Department and the WHO Regional Office for Africa.

2.4 THE IVR MATRIX

IVR staff members are responsible for one or more vaccines against priority diseases in line with their expertise. In this manner, their work often spans both product development and implementation research (Table 1).

BOX 2. EXAMPLE OF IMPLEMENTATION RESEARCH IN PARTNERSHIP WITH GAVI: ACCELERATED DEVELOPMENT AND INTRODUCTION PLANS

Vaccines against two of the most severe agents of child mortality – rotavirus and pneumococcus – have now been licensed, and targeted projects called Accelerated Development and Introduction Plans (ADIPs) will accelerate access of developing countries to these potentially life-saving novel vaccines. IVR is a strategic partner of the ADIPs and will further complement this work by taking a broader perspective on the rotavirus and pneumococcus vaccine research agenda, promoting support for the evaluation of early stage products, and investigating neonatal and alternative vaccination schedules.

BOX 3. EXAMPLE OF AN HVI HIGHLIGHT: THE AFRICAN AIDS VACCINE PROGRAMME

The African AIDS Vaccine Programme (AAVP) was conceived in 2000 as a network of African experts and communities. AAVP promotes vaccine development and the evaluation of promising HIV candidates in Africa by building on local knowledge and resources, and by encouraging collaboration among African countries, as well as with other countries and partners internationally. AAVP's activities focus on its areas of comparative advantage and aim to respond to needs and gaps identified in advocacy, capacity strengthening, and in ethical, regulatory and legal frameworks for HIV vaccine clinical trials in Africa to ensure that the best vaccine candidates are tested in the most appropriate clinical sites. To this end, AAVP supports the development of National HIV Vaccine Plans. In 2006, following recommendations arising from the Yaoundé Statement*, the AAVP launched a new five-year strategic plan to better align the programme's strategic orientations with those of the Global HIV Vaccine Enterprise, while maintaining a high level of visibility for AAVP and ensuring that the African perspective on HIV vaccine R&D is fully taken into account.

* *Accelerating the Global Effort for HIV Vaccine Research: Report of the Third Forum of the African AIDS Vaccine Programme, Yaoundé, Cameroon, 17-19 October 2005*. Geneva, WHO and UNAIDS, 2006 (WHO/IVB/06.07).

TABLE 1. CURRENT IVR VACCINE RESEARCH CATEGORIZED BY PRODUCT DEVELOPMENT OR IMPLEMENTATION RESEARCH, WITH MAIN IVR PARTNERS AND COLLABORATORS

Category	Disease/ pathogen or project	Product development[a]	Implementation research	Main strategic partners and collaborations[b]
Major poverty associated infectious diseases	HIV	✓	✓	ANRS, BMGF, CDC, EDCTP, GHVE, IAVI, NIH, UNAIDS, WRAIR
	Malaria	✓	✓	BMGF, EDCTP, EMVI, EU, MVI, NIH, RBM, TDR, USAID, Wellcome Trust
	Tuberculosis (non-BCG)	✓	✓	Aeras, BMGF, EU, NIH, Stop TB
Acute respiratory infections	*Haemophilus influenzae* B		✓	CDC, GAVI Hib Initiative, LSHTM NIAID
	Influenza (broad spectrum)	✓	✓	BMGF, WHO
	Pneumococcus	✓	✓	BMGF, CDC, EU, LSHTM, MRC, NIAID, PATH, PneumoADIP, USAID
Diarrhoeal diseases	Cholera		✓	BMGF, IVI, NIH
	Enterotoxigenic *E coli*	✓		CVD, Göteborg University, Institut Pasteur
	Rotavirus	✓	✓	BMGF, CDC, MCRI, PATH, RAPID, USAID
	Shigellosis	✓		CVD, IVI, NIH, WRAIR
Flaviviruses	Dengue	✓	✓	BMGF, PDVI , WRAIR
	Japanese encephalitis	✓	✓	JE Project at PATH, WRAIR
Other diseases/projects	Cervical cancer (human papilloma virus)	✓	✓	BMGF, Harvard University, IARC, NIH, PATH
	Hepatitis B		✓	WHO
	Measles (aerosol)	✓	✓	ARC, BMGF, CDC
	Meningitis (*Neisseria meningitidis*)	✓	✓	BMGF, MVP
	Rabies (for immunoglobulins)	✓		WHO Collaborating Centres
	Rubella		✓	CDC
	New technologies	✓		PATH, Rockefeller, Wellcome Trust

[a] As highlighted in Fig. 6, IVR's role in research and product development is either as a developer, or a facilitator

[b] See Abbreviations of vaccine research sponsors and partners on page ii

3. IVR STRATEGY AND EXPECTED RESULTS

3.1 PRIORITY SETTING

The limitation of resources, the challenges of emerging or re-emerging pathogens, as well as changes in the technical, political and regulatory environments, make it essential to prioritize efforts on a logical, evidence-driven basis. Decisions on the diseases and vaccines that form IVR's portfolio, i.e. those to which human and financial resources are devoted, are based on a decision-tree approach followed by a qualitative assessment to determine the type of research in which IVR may engage. Decisions and priority-setting for new vaccine delivery technologies are taken following consultation with the relevant steering committee or product advisory group.

3.1.1 THE DECISION TREE

The key questions IVR asks before deciding on its involvement in vaccine R&D, illustrated in Figure 4 below, relate to the following:

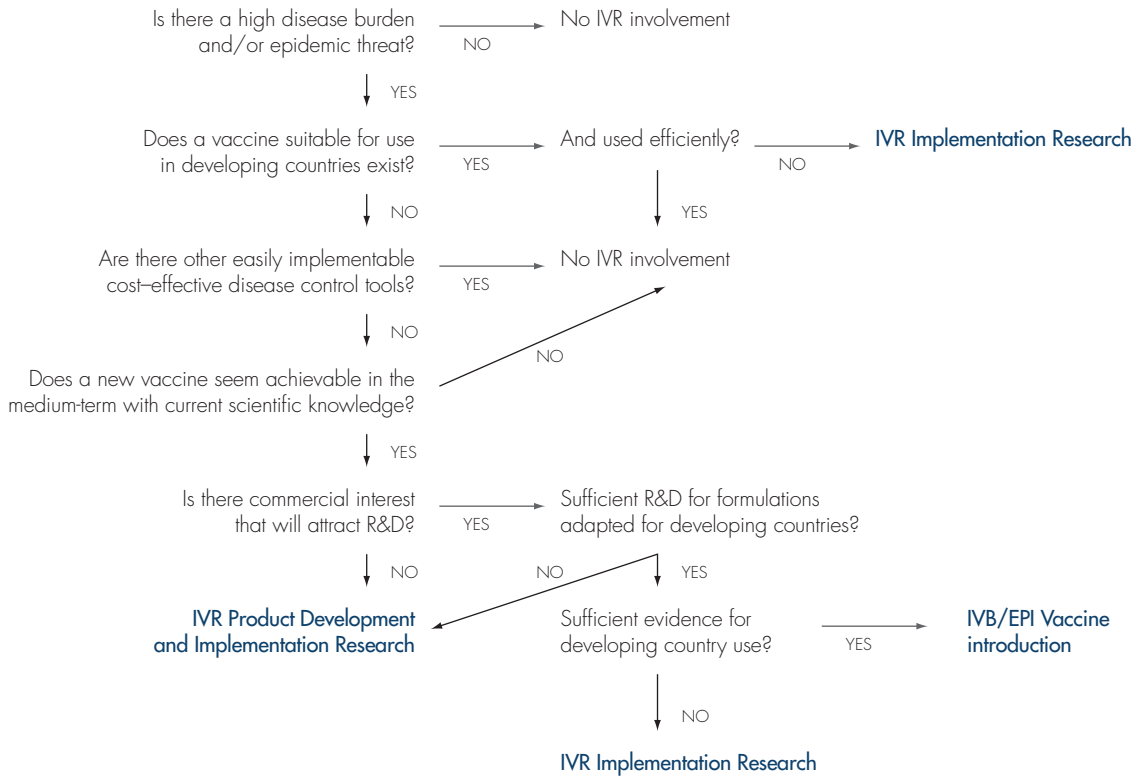
- the public health relevance, i.e. disease burden (global or regional), epidemic threat and relevant recommendations from the World Health Assembly;
- the availability of a vaccine that is suitable and affordable for widespread use in developing countries;
- the existence of other efficient, accessible and sustainable disease control tools;
- the existence of sufficient scientific knowledge to allow development of a vaccine in the short- or medium-term;
- the existence of sufficient commercial potential in a vaccine to attract appropriate resources to develop it for global use; and
- the existence of sufficient information to allow prioritization of the vaccine in national immunization programmes.

3.1.2 QUALITATIVE ASSESSMENT

While this process allows the identification of diseases and associated vaccines that are eligible for IVR attention, it results in a portfolio that cannot be fully accommodated within the resources available in IVR. Hence, a qualitative assessment of the potential impact IVR could make, including a more detailed analysis of each element, is conducted to refine the prioritization. The magnitude of the disease burden, for example, or the risk of a large epidemic is considered. Furthermore, the cost–effectiveness of an immunization programme compared to other control measures, combined with an analysis of the obstacles to vaccine development and/or implementation, also need detailed evaluation. Noting areas where WHO input would be critical, and the Organization's comparative advantage relative to other possible sources, are important considerations in the prioritization process.

Some diseases are not subject to any priority setting exercise. This is the case when the priority for vaccine R&D has already been examined by one of IVR's constituencies (TDR or UNAIDS) or when there is a mandate from the World Health Assembly. For example, WHO's commitment to reach measles mortality reduction objectives means that the development of an aerosol

FIG. 4 IVR DECISION TREE FOR VACCINE RESEARCH



measles vaccine formulation is a high priority for IVR even though an effective inexpensive parenteral vaccine against measles already exists.[1] Several other diseases associated with a high epidemic threat, such as influenza and Severe Acute Respiratory Syndrome (SARS), also circumvent further prioritization exercises.

Decisions to add new vaccine initiatives or target diseases to the IVR portfolio, or to change the priority or role of IVR for those already in the portfolio, are implemented following approval by the IVR Vaccine Advisory Committee. Figure 5 below presents the list of diseases of current priority interest to IVR.

[1] Resolution WHA56.20 "Reducing global measles mortality" in 2003 reflects the objectives set by the United Nations Assembly Special Session on Children in 2002 (resolution S-27/2, annex) and the UN Millennium Development Declaration (General Assembly resolution 55/2 in 2000).

FIG. 5 PORTFOLIO OF DISEASES FOR VACCINE R&D CONSIDERATION

Acute respiratory disease associated with respiratory syncytial virus
Acute viral gastroenteritis (calciviruses)
AIDS
Buruli ulcer
Cervical cancer (human papilloma virus)
Cholera
Dengue
Enterotoxigenic *Eschericha coli* diarrhoea
Gastric cancer *(Helicobacter pylori)*
Genital herpes (HSV-2)
Haemophilus influenzae type b meningitis
Hepatitis B
Hookworm disease
Influenza
Japanese encephalitis
Leishmaniasis
Leptospirosis
Malaria
Measles
Meningococcal meningitis (*Neisseria meningitides* types A,C,W135
Pneumococcal pneumonia (*Streptococcus pneumoniae)*
Poliomyelitis
Rabies
Rotavirus diarrhoea
Rubella
Schistosomiasis
Severe Acute Respiratory Syndrome
Shigellosis
Group A and B *Streptococcus*
Trachoma
Tuberculosis
Typhoid fever
West Nile fever

The next paragraphs illustrate how these priority diseases are addressed within the three major objectives – or Expected Results – of IVR.

3.2 IVR EXPECTED RESULTS

WHO has used results-based management to prepare its Programme Budget and activities since the year 2000. The Secretariat of the Organization is collectively accountable for achieving the Organization-wide Expected Results set out in the Programme Budget. All WHO efforts on vaccine R&D are geared towards the following Expected Result:

> "Research supported, guidance provided, partnerships built and research and development capacity in developing countries strengthened for the development of vaccines against infectious diseases of public health significance."

WHO headquarters and country and regional offices contribute to its achievement through the setting of expected results at their respective level of the Organization. Planning, performance monitoring and assessment, and reporting must all relate to these specific Expected Results. IVR has set itself the following Expected Results for 2006–2009, which are discussed in detail below.

- 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 appropriate implementation research and development of tools to support evidence-based recommendations, policies and strategies for optimal use of vaccines and technologies.

3.2.1 MANAGEMENT OF KNOWLEDGE AND PROVISION OF GUIDANCE AND ADVOCACY THROUGH EFFECTIVE PARTNERSHIPS TO ACCELERATE INNOVATION FOR NEW AND IMPROVED VACCINES AND TECHNOLOGIES

Given that new or improved vaccines and immunization-supporting technologies are regularly becoming available, IVR has a responsibility to maintain an overview of information on their status. This collective information reservoir forms the basis of guidance and advocacy, and allows countries to make informed decisions. Where possible, partnerships are established to accelerate development and introduction of new vaccines and technologies.

PRIORITY ACTIVITIES FOR KNOWLEDGE MANAGEMENT

This IVR Expected Result will be achieved by concentrating on knowledge, research and portfolio management; and analysis of intellectual property rights issues. A number of priority activities will support IVR's mission to promote innovation and the operational vision to facilitate the vaccine R&D pipeline, notably:

- periodic review of the latest scientific advances, as well as of relevant innovations and technologies;
- participation in the harmonization of internationally accepted quality standards and regulatory requirements used in R&D;
- promotion of community participation in vaccine development;
- review and analysis of intellectual property rights issues relevant for vaccine R&D;
- review of clinical trial protocols submitted for advice by partners and countries;
- organization of broad consultations on ethical issues arising during the conduct of clinical trials;
- creation and maintenance of a database of clinical trial sites and GMP-compliant manufacturers;
- coordination of repositories (e.g. the WHO-UNAIDS repository of HIV reagents);
- translation of research findings into publications and media communications to ensure the broad dissemination of knowledge and to provide for advocacy needs;
- wide dissemination of information about adjuvants on the Internet; and
- organization of the annual Global Vaccine Research Forum and other conferences and workshops that bring together the global vaccine R&D community for discussions on the latest developments in the field, and promote networking.

IVR actively builds partnerships and networks to support the global vaccine pipeline. The African AIDS Vaccine Programme and the TB Vaccine Working Group within the Stop TB Partnership are particularly successful IVR-facilitated networks to accelerate innovation for new and improved vaccines (see Boxes 3 and 4).

IVR's main collaborators can be categorized as follows:

- industrialized and developing country researchers, research institutions and nongovernmental organizations;
- public–private partnerships
- disease control programmes;
- global partnerships such as the GAVI Alliance, Roll Back Malaria and Stop TB;

BOX 4. EXAMPLE OF KNOWLEDGE MANAGEMENT: TUBERCULOSIS VACCINES

Around one-third of humanity is currently infected with tuberculosis (TB), the vast majority of whom live in developing countries. A vaccine working group has now been established within the Global Partnership to Stop TB, for which IVR provides the Secretariat. The goal of this coalition of international partners is to facilitate the control – and ultimate elimination – of TB as a public health problem. The first TB vaccine candidates have progressed from preclinical development to clinical evaluation in humans and preliminary scientific results give hope that new effective TB vaccines may be introduced within the next ten years. IVR's current focus includes the definition of immunological and clinical end-points, and target product profiles.

- pharmaceutical and biotechnology industries, both in industrialized and developing countries;
- international donors and foundations; and
- offices of the United Nations and its Specialized Agencies;

All WHO collaboration with third parties, including industry, focuses on ensuring broad access at preferential prices to new vaccines and technologies for the public sector of developing countries. In this framework, IVR fosters interaction with the private sector from both developing and industrialized countries in a transparent and accountable way and on a competitive, non-exclusive basis. The terms of such collaboration are usually stipulated in a Memorandum of Understanding or Exchange of Letters.

The following indicator will measure progress towards IVR's knowledge management expected result (see also Section 4 for disease and technology specific milestones):

Indicator	Status Jan 2006	Target for end 2007	Target for end 2009
Number of vaccine research agendas established for four priority diseases, through broad consultation with developing countries and research partners, and endorsement by the IVR Vaccine Advisory Committee.	0 of 4	2 of 4	4 of 4

3.2.2 SUPPORT TO RESEARCH AND PRODUCT DEVELOPMENT FOR WHO PRIORITY NEW VACCINES AND TECHNOLOGIES

The ability to produce vaccines relies on the discovery and development of antigens into effective products that can be introduced broadly into immunization programmes. Priority is given to vaccines that have the greatest potential impact on public health, and that can be produced by several vaccine manufacturers.

IVR's role is either to develop or to facilitate research and product development, depending on which is considered to have the biggest impact. Figure 6 lists the current IVR vaccine activities according to the type of support provided.

IVR AS A DEVELOPER

IVR acts as a "developer" when a potential candidate vaccine lacks R&D investment and leadership, and where an active role of IVR in product development will benefit the vaccine pipeline for the disease in question. In such cases, IVR will dedicate human and financial resources to specific projects, and combine its own strengths with those of other developers by directly supporting certain associated research and management tasks, and/or by forging collaborations and co-sponsorship relationships.

For vaccines or technologies where IVR is a developer, a virtual team is established to drive product discovery,

FIG. 6 TYPE OF IVR INVOLVEMENT IN VACCINE RESEARCH AND PRODUCT DEVELOPMENT

IVR is a developer for	IVR is a facilitator for
Measles (aerosol)	AIDS
Meningitis A,C,W135	Cervical cancer (human papilloma virus)
Rabies	Cholera
Needle-free technologies	Dengue
	Enterotoxigenic *Escherichia coli*
	Influenza
	Japanese encephalitis
	Leishmaniasis
	Malaria
	Rotavirus diarrhoea
	Shigellosis
	Streptococcus A
	Streptococcus pneumoniae
	Tuberculosis

development and licensing for the developing country market. Public–private partnerships are formed if no manufacturer is taking full ownership for all the elements necessary to develop and license a new product. Such partnerships are also formed for programmes developing vaccines that are tailor-made for defined populations within a region. An example of IVR support as a developer is the Measles Aerosol Vaccine project (see Box 5).

IVR AS A FACILITATOR

IVR fulfils a "facilitator" role when many funding agencies and product development programmes or support structures are already active in the vaccine R&D pipeline. In this situation, IVR impacts on the associated environment rather than on building the individual components of the R&D pipeline itself (see Box 6). As a facilitator, IVR does not sponsor the development of specific vaccine candidates, but supports global research and product development as an independent, objective, process consultant and strategic or technical adviser. In terms of financial involvement, IVR can provide seed funds, bridging support, or resources to developing countries for research that is needed for future vaccine introduction.

In some instances, while being a facilitator, IVR may host individual development projects if, for example, they are recommended by the IVR Vaccine Advisory Committee or one of the thematic steering committees, provided that the project is fully supported by existing designated funds and human resources. Such projects, although part of IVR, are considered independent from, and subsidiary to other activities facilitating global vaccine development. IVR support to the malaria vaccine candidate PfCP2.9 is an example of this type of activity.

Diseases move through the priority list as the global vaccine R&D pipeline develops and partnerships strengthen, either by entry or exit from the IVR portfolio, or by moving between the developing and facilitating

BOX 5. EXAMPLE OF IVR AS A DEVELOPER: THE MEASLES AEROSOL PROJECT

Measles kills over 390 000 children per year, mainly in developing countries, and represents a significant proportion of the vaccine-preventable child mortality burden. The measles vaccine is very efficient and cost effective. However, it requires high immunization coverage supported by mass catch-up campaigns to reduce the remaining disease burden.

Several promising methods for respiratory delivery of currently licensed measles vaccines, such as jet nebulizers, piezoelectric nebulizers, nasal sprays and dry powders, have been developed and tested. Because the vaccines will be delivered by a different route, detailed studies must be performed to ensure that the vaccine already licensed for subcutaneous injection is as safe and efficacious by the respiratory route before it is licensed for this route. Although some studies have been performed, the comprehensive testing necessary to license a particular device for widespread use has not yet been undertaken.

The goal of the Measles Aerosol Project is to license at least one method for respiratory delivery of vaccines currently licensed for subcutaneous delivery. This will provide a means of administering measles vaccine that is safer and easier than injection. At least three devices for aerosol administration of reconstituted vaccine and, if feasible in the time frame, a dry powder device, will be evaluated.

BOX 6. EXAMPLE OF AN IVR FACILITATOR PROJECT: GENERATING AN ENABLING ENVIRONMENT FOR HUMAN PAPILLOMA VIRUS VACCINE DEVELOPMENT AND GLOBAL INTRODUCTION

In coordination with partners, IVR aims to protect women in developing countries against human papilloma virus (HPV) infection. HPV is associated with over 99% of all cases of cervical cancer which, today, is only partially controlled through prevention screening methodologies, and even then only in industrialized countries. A safe and efficacious HPV vaccine, complemented by screening, could improve cervical cancer prevention. Two HPV candidate vaccines are in Phase III clinical trials, although much work needs to be done before these vaccines are accessible to the majority of developing countries. IVR has initiated several facilitating activities to accelerate the process of global vaccine introduction:

- harmonizing and standardizing laboratory procedures and creating a global HPV Laboratory Network to facilitate vaccine licensing and monitoring in developing countries;
- generating an enabling environment for future HPV vaccine introduction by creating an international multi-disciplinary policy platform and setting a global agenda in consultation with regions and countries;
- creating a WHO Information Centre on HPV and Cervical Cancer to facilitate global, regional and national decisions on current and novel options for cervical cancer prevention.

type of IVR support if an opportunity for research and/or partnerships should arise.

PRIORITY RESEARCH AND PRODUCT DEVELOPMENT ACTIVITIES

Activities in support of the expected result for research and product development fall within the following fields, which are described below:

- antigen discovery;
- product development;
- development and evaluation of new technologies;
- strengthening of capacity in developing countries for vaccine production and evaluation; and
- support to and optimization of clinical trials.

Antigen discovery is critical to fuel the neglected diseases R&D pipeline with vaccine candidates. As discussed in the Introduction, statistically probable success of producing one licensed product requires at least four independent vaccine candidates to be under development at any one time. Antigen discovery stimulates an increase in the number of new vaccine candidates. As in past years, IVR will provide financial support either for the identification or modification of new antigens, or for their early validation in animal models or in vitro systems.

The **product development** area covers both developer and facilitator activities for IVR priority vaccines. Product development is an essential step between vaccine discovery and production. It entails preclinical and clinical testing, optimization of the proposed production process and fine tuning of the composition or formulation of the vaccine candidate. While product development is a very costly operation, IVR can provide vaccine developers with expert advice as well as seed funds that allow leverage of more

substantial resources and gathering of evidence for the feasibility of scaling up vaccine candidate production.

Development and evaluation of new technologies focuses on the identification and development of novel technologies to improve either the immunogenicity or the delivery of vaccines. Challenges to be addressed include: ensuring immunization safety by reducing and ultimately eliminating problems associated with the use of needles and syringes; improving the heat stability of vaccines to render immunization programmes less "cold chain reliant"; reducing the number of doses required for full immunity, and thus the number of visits to health centres; and improving the utilization of adjuvants to optimize the efficacy of existing vaccines and those under development. With the advice of a Steering Committee of independent experts, technological barriers to improved vaccination logistics and safety are identified and solutions investigated (see Box 7). IVR will continue to identify novel technologies, prioritize them, and provide seed funds for research that could lead to the development of those applicable in developing countries.

Grass-roots research capability in disease endemic countries not only contributes to the sustainability of R&D processes, but also secures subsequent research support for successful vaccine introduction. The most appropriate clinical trial sites are most often located in regions where disease incidence is high and where the vaccine, if effective, is likely to be used in the future. However, many clinical sites in these regions have neither previous experience in applying Good Clinical Practice (GCP) nor the capacity to conduct a proper ethical review. As a collaborator or sponsor of vaccine clinical trials, IVR (in association with TDR and international partners) is therefore building or strengthening the capacity of selected clinical trial sites to conduct vaccine studies in agreement with the highest GCP and bioethics review standards. WHO's regional offices will facilitate the coordination of **research capacity strengthening** in developing countries.

Support to and optimization of clinical trials aims to facilitate the clinical evaluation of new vaccines against priority diseases. Activities include, inter alia, the development of generic protocols, the development

BOX 7. EXAMPLE OF AN IVR TECHNOLOGY PROJECT: NEEDLE-FREE VACCINE DELIVERY

A recurrent problem with traditional parenteral vaccination using needles is the transmission of blood-borne pathogens through the reuse of needles and the inadvertent needle-stick injuries that occur during delivery of the vaccine or through improper waste disposal.

Needle-free parenteral delivery would make vaccination easier and safer, and could potentially improve coverage rates. Single-use cartridge jet injectors may be the solution. Prototype high-speed jet injectors with auto-disable safety features aimed at mass immunization were evaluated for user acceptability in South Africa and the United Republic of Tanzania. The results of these studies led IVR to prefer the development of smaller, lighter and less expensive designs that could be used in routine and campaign immunization in developing countries. Future activities will compare the clinical demonstration of the safety and immunogenicity of jet injector-delivered vaccines to conventional delivery with vaccines such as tetravalent DTP-HepB.

of new assays and methods to evaluate the efficacy of specific candidate vaccines, the standardization and validation of existing assays, studies to combine different assays into a unified correlate of protection, and the development of a consensus definition of relevant clinical end-points. The success of these activities is critical for the comparison of clinical results obtained by different investigators in different epidemiological settings. As a facilitator, IVR is well positioned to provide a forum for the various stakeholders, where broad agreement around the above issues can be reached.

The following indicators will measure progress towards IVR's research and product development expected result (see also Section 4 for disease and technology specific milestones):

Indicator	Status Jan 2006	Target for end 2007	Target for end 2009
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	3 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 (where IVR is involved in clinical trials).*	1 of 6	5 of 6	6 of 6

* Clinical trial completed or ongoing, with a satisfactory report of Good Clinical Practice from a WHO independent monitor

3.2.3 CONDUCT OF APPROPRIATE IMPLEMENTATION RESEARCH AND DEVELOPMENT OF TOOLS TO SUPPORT EVIDENCE-BASED RECOMMENDATIONS, POLICIES AND STRATEGIES FOR OPTIMAL USE OF VACCINES AND TECHNOLOGIES

New – or updated – vaccination policies need to be driven by evidence that they will make a positive impact. Thus, relevant operational and cost–effectiveness research and modelling of data need to be conducted to inform these policy decisions.

IVR implementation research aims to: build evidence and optimize delivery strategies to support decisions for introducing new or under-utilized vaccines into national immunization programmes in developing countries (Figure 7). As with research and product development, IVR's implementation research activities are prioritized according to the most beneficial contribution it can make.

PRIORITY IMPLEMENTATION RESEARCH ACTIVITIES

Activities in support of the implementation research expected result fall within the following fields, which are described below:

- development of tools and models to assess disease burden, cost–effectiveness and impact of vaccines and delivery strategies;

FIG. 7 IMPLEMENTATION RESEARCH PRIORITIES

Maturity of vaccine	
Traditional vaccines	Potential, new or underused vaccines
BCG	AIDS
DTP (diphtheria, tetanus and pertussis) combinations	Cervical cancer (human papilloma virus)
Measles	Cholera
	Dengue
	Haemophilus influenzae B meningitis
	Hepatitis B
	Japanese encephalitis
	Malaria
	Meningitis (*Neisseria meningitidis*)
	Rotavirus diarrhoea
	Rubella
	Acute respiratory infection associated with *Streptococcus pneumoniae*
	Tuberculosis (non-BCG)

- design and conduct of vaccine and new technology effectiveness trials;
- design and conduct of vaccine and new technology acceptability studies; and
- development of models to estimate the impact of multiple interventions, including vaccination, against infectious diseases.

Development of tools and models to assess disease burden, cost–effectiveness and impact of vaccines and delivery strategies. Estimates of the burden of vaccine-preventable diseases are essential for prioritizing global efforts in the field of vaccines and immunization. They are also required to monitor and assess progress and to calculate the return on investment generated by vaccination. IVR plays a key role in developing burden estimates at global, regional and country levels using the best available data and mathematical models. In certain countries with little data, estimates are often derived from information from neighbouring countries or from similar country groupings. In cases where such data are inadequate for local decision-making or for monitoring vaccine impact at the national level, the implementation of generic tools to develop national data will be undertaken primarily through WHO's regional offices with technical support from IVR.

Information on cost–effectiveness is a key component of rational decision-making in both industrialized and developing countries, but especially in countries with fewer resources and competing health priorities. Within the context of generating the evidence to prioritize vaccine introduction into national immunization programmes, IVR develops standardized tools to allow countries to determine the cost–effectiveness of new vaccines.

This line of research is particularly relevant in preparing the public sector to ensure rapid global access to future HIV vaccines (Box 8). Indeed, the existing paradigms for HIV/AIDS drug development clearly demonstrate the negative consequences of waiting for product licensing before assessing critical access issues. IVR is well placed to ensure that a number of urgent and pertinent issues are resolved, and is committed to developing policies to guide national decision-making on the introduction of future HIV vaccines.

Design and conduct of vaccine and new technology effectiveness trials. The effectiveness of some vaccines, especially live oral vaccines, may vary considerably between children in developing and industrialized countries. Hence, it is essential to establish the effectiveness of the vaccines in representative populations in developing countries. In the past, such evaluations were usually undertaken several years after the vaccine was introduced. Furthermore, efficacy studies in industrialized countries use outcomes that are important to them, whereas the disease priorities in developing countries may be quite different. For example, a pneumococcal conjugate vaccine was licensed in the USA on the basis of efficacy against pneumococcal disease and primary febrile bacteraemia. Febrile bacteraemia is not a priority in most developing countries whereas pneumonia, which is mostly caused by pneumococcus, is. Demonstration of the extent to

BOX 8. EXAMPLE OF AN IMPLEMENTATION RESEARCH PROJECT: DELIVERY AND COST–EFFECTIVENESS STUDY FOR HIV VACCINES

IVR sponsored a study to assess national preferences and expectations for future HIV vaccines* and to estimate the cost–effectiveness of vaccination programmes in different country and epidemiological settings.

The study used a questionnaire to ask five countries (Brazil, China, Kenya, Peru and Thailand) to describe their current vaccine delivery capacity and the profile they would find acceptable for potential HIV vaccines. Countries were also asked to explain criteria for selecting potential target groups for vaccination, and describe strategies to reach them. Findings showed that countries have vastly different expectations and criteria for HIV vaccines introduction and deployment.

A modelling study was also undertaken to estimate the population-level impact and cost of an HIV vaccine under various scenarios. One aim of a vaccine model is to find the "critical vaccination fraction", which defines the population size that would need to be vaccinated in order to break the virus transmission chain, thus halting the epidemic. The general conclusions of the research showed that the epidemic could be controlled with a moderately effective vaccine, and that such an intervention could be cost–effective.

Key informants included government health officials, practitioners, NGO representatives, community leaders involved in HIV or EPI programmes, and those generally well-informed on HIV, AIDS and vaccines.

* It is acknowledged that the first HIV vaccines are likely to slow down the onset and evolution of the disease, rather than provide 100% protection against infection.

which the vaccine reduces pneumonia is therefore important before it can be prioritized for use in developing countries. Ensuring that vaccines are evaluated in a timely manner in developing countries and against disease syndromes of public health importance for these countries is part of the IVR implementation research workplan.

In addition, many vaccines developed and licensed for use in industrialized countries are evaluated using immunization schedules that may differ from those used in developing countries, or may not protect a significant proportion of the susceptible population in countries where infectious diseases tend to occur at an earlier age. For some vaccines, especially the polysaccharide-protein conjugate vaccines, higher antibody responses are seen in infants in developing countries. Thus, it is possible that schedules using fewer doses, given at a more appropriate age, may be equally effective and less expensive. Evaluation of alternative schedules or strategies for effectively delivering immunization at lower cost is another component of the IVR implementation research portfolio (Box 9).

Design and conduct of vaccine and new technology acceptability studies. The introduction of new vaccines into immunization programmes needs to take into consideration the acceptability for the target population of the proposed product, delivery method and schedule of vaccination. For example, certain groups may consider vaccines against HPV infection and cervical cancer as potentially inducing adolescents to sexual promiscuity. Indeed, HPV is a sexually transmitted pathogen, and effective immunization should target individuals before the onset of sexual activity. IVR therefore gives the utmost importance to analysing the acceptability of the vaccine in particular communities before designing strategies for its widespread introduction. Another example relates to studying the willingness of parents and children to replace parenteral

BOX 9. EVALUATION OF ALTERNATIVE VACCINATION SCHEDULES FOR PNEUMOCOCCAL CONJUGATE VACCINES

Streptococcus pneumoniae (pneumococcus) is a common cause of morbidity and mortality worldwide, most of the latter occurring in young children in developing countries. Prevention of disease by vaccination is one of the most promising and cost–effective approaches to controlling this burden of disease. A 7-valent glycoprotein conjugate vaccine is used in the routine infant immunization programme in the USA and has resulted in a dramatic reduction in the severity of disease, not only in the immunized population but also in other age groups due to the herd immunity effect. New conjugate vaccines containing additional serotypes of pneumococcus have shown efficacy in preventing invasive disease and pneumonia in the Gambia and South Africa, both in HIV-infected and non-infected infants. IVR's objective is to undertake activities that will facilitate the introduction of these life-saving vaccines in developing countries that carry the highest burden of disease. This objective is shared by GAVI's PneumoADIP at Johns Hopkins.

In the industrialized world, minimizing the costs associated with immunization through a reduced number of doses to establish effective immunity is a relatively minor issue. However, developing country immunization programmes are tightly constrained by cost, and regimens with one or two, rather than three doses of a vaccine would be a great advantage. In addition, the current cost of conjugate pneumococcal vaccines is substantially higher than that of traditional EPI vaccines, making evaluation of a reduced dose series a necessity. IVR is promoting two safety and immunogenicity studies in infants on alternative vaccination schedules, the final results of which are expected in 2006–2007.

with mucosal vaccination before embarking on large-scale immunization campaigns with an aerosol measles vaccine formulation.

Development of models to estimate the impact of multiple interventions, including vaccination, against infectious diseases. Implementation research is needed not only to improve schedules, combinations and operational practices, but also to better integrate immunization into diverse health system scenarios. Mathematical models can support national decision-making on immunization strategies. One such model aims to demonstrate that adding a school-based tetanus immunization programme for 6–8 year olds results in increased protection from neonatal tetanus in future births. Another example is the development of models to compare the impact and cost–effectiveness of different ways of delivering a second dose of measles vaccination. Such models are typically based on previously collected data, but they do require some "real world" validation, particularly when the underlying data and assumptions are not directly applicable to the settings in which they will be employed. In order to minimize the number of costly real world demonstration trials, IVR has prioritized analytical research supported by ad-hoc, small-scale field research.

As expressed in the Global Immunization Vision and Strategy, this area of activity includes qualitative research to improve understanding of factors influencing vaccine uptake and coverage, and contributes to the development of gender-sensitive strategies to reach more people with life saving-vaccines.

The following indicators will measure progress towards IVR's implementation research expected result (see also Section 4 for disease and technology specific milestones):

Indicator	Status Jan 2006	Target for end 2007	Target for end 2009
Number of new vaccines (particularly pneumococcal, meningococcal A, Japanese encephalitis, rotavirus, human papilloma virus) for which evidence has been generated on the appropriateness for introduction into immunization programmes.	0 of 5	2 of 5	5 of 5
Number of targeted countries where pilot testing of a tool to estimate cost–effectiveness of HIV vaccines has been completed (Brazil, China, Kenya, Peru, Thailand)*.	2 of 5	5 of 5	—

* The selection of countries for pilot testing ensures geographical representation of the data generated and is driven by the availability of competent sites to conduct the study.

4. IVR ACTIVITIES AND MILESTONES 2006–2007

This section provides a brief overview of how IVR sees its role and comparative advantage – by disease or technology – during 2006 and 2007, indicating the main milestones (bullets) which will be used to determine success.

4.1 AIDS, MALARIA, TUBERCULOSIS

AIDS

HVI/IVR will maintain its role as facilitator and impartial broker in support of global efforts to promote HIV vaccine R&D, ensuring that vaccine-related research and HIV vaccine trials are conducted at the highest scientific and ethical standards. Focus will continue on the needs of developing countries, which bear the largest burden of the HIV pandemic. More specifically, HVI will facilitate: scientific, technical and ethical guidance; international reference reagents for vaccine development; National HIV Vaccine Plans, particularly in AAVP target countries; and guidelines to assess the cost–effectiveness of HIV vaccination strategies for public health use.

- Normative guidelines are developed and provided to selected countries conducting HIV vaccine clinical trials (end 2006).
- Tools to assess the cost–effectiveness of HIV vaccination strategies are developed and validated in six target countries (end 2006).
- International reference reagents for HIV vaccine development are disseminated (2006–2007).
- Support is provided to five AAVP target countries for the development and implementation of National HIV Vaccine Plans (end 2007).

MALARIA

IVR remains committed to providing technical support for R&D of selected candidates among the impressive number currently in the pipeline. However, its overall strategy in 2006–2007 will give increased priority to normative activities, notably guidance on the preclinical and clinical evaluation of candidates in adherence with rigorous scientific, safety and regulatory principles. It is recognized that scientific and technical consensus will be needed on issues such as measures of vaccine efficacy, impact on disease burden indicators and comparative advantages of focusing on other malaria or health-related interventions. The role of IVR is therefore to ensure that sound and credible research and analysis form the backbone of evidence in order to inform decision- and policy-making on the development of malaria vaccines.

- At least one new clinical trial site in a disease-endemic area is assessed and ready to carry out Phase Ib/II trials (2006).
- A framework for decision-making in standard of care for participants in vaccine trials is published (2007).
- A reference standard reagent for AMA1 ELISA is available (2007).
- Case definitions for clinical trial end-points for uncomplicated and severe malaria are available (2007).
- The results of the second PfCP-2.9 Phase I clinical trial are submitted for publication (2007).

TUBERCULOSIS

The 2006–2007 biennium will be a turning point for TB vaccine development activities. Some preclinical activities, e.g. on standardized animal models, will be brought to a conclusion, while clinical evaluation and other, more downstream aspects, will gain in importance. These include IVR's work on immunological and clinical end-points, and on target product profiles. The involvement of endemic countries in evaluating new TB vaccines will be critical, as will a focus on pre-introduction activities such as economic studies, the evaluation of needs, and opportunities for new TB vaccines in high-burden countries. IVR will continue to provide information and technical support to national health authorities to assist them in these analyses.

- A resource and training centre for the evaluation of immunological end-points in TB vaccine trials is established (end 2006).
- Consensus on standard clinical end-points in TB vaccine efficacy trials is reached (end 2006).
- Target product profiles for new TB vaccines (one pre-exposure and one post-exposure) are defined (end 2007).
- A TB vaccine evaluation and introduction plan is developed with one African and one Asian TB high-burden country (end 2007).

4.2 ACUTE RESPIRATORY DISEASES

INFLUENZA

Studies will continue on the standardization of immunological assays and evaluation of pandemic vaccines in clinical trials. The safety and efficacy of vaccines using alternative routes of administration of influenza vaccines, including mucosal and intradermal applications, will also be assessed.

- Data on the clinical evaluation of candidate pandemic influenza vaccines are available (mid 2006).
- New functional and simpler methods for evaluating T-cell immune responses induced by influenza vaccines are developed (early 2007).
- Improved, standardized techniques to evaluate immune responses in the respiratory tract are initiated (mid 2007).
- A standardized microneutralization assay protocol for influenza virus and a panel of reagents to perform and quality assure the test are established at a WHO Collaborating Centre (2007).

PNEUMOCOCCAL PNEUMONIA

Over the next two years, IVR aims to complete the updated, validated estimates of the global and regional burden of pneumococcal disease and initiate the process of country consultation to validate national estimates. In collaboration with its regional and country offices and the PneumoADIP, WHO will assist countries to generate high-quality disease burden data by strengthening existing surveillance networks and making available a validated disease burden assessment tool. Cross-laboratory standardization of multiplex killing assays to measure immune response to vaccination will be undertaken. These assays will allow comparison between different vaccine candidates, including conjugate and common protein vaccines. Finally, guidelines for the clinical evaluation of new candidate vaccines, including protein-based vaccines, will be established.

- Official WHO global and regional pneumococcal disease burden estimates are published (end 2006).
- Guidance is provided to developing country vaccine manufacturers on appropriate valency for effective, affordable conjugate pneumococcal vaccines (end 2006).

- IVR technical support and WHO regional office coordination of networks have enabled information to be available on serotype distribution of the organism causing severe disease in all WHO regions, based on data from numbers of isolates comparable to those in western European countries (end 2007).
- The trial evaluating a schedule with a birth dose of pneumococcal conjugate vaccine is completed (end 2007).
- At least one trial evaluating alternative schedules using fewer doses of pneumococcal conjugate vaccine is completed in two developing country populations (end 2007).

4.3 DIARRHOEAL DISEASES

ENTEROTOXIGENIC *ESCHERICHIA COLI* (ETEC)

WHO will focus on facilitating the research field through organizing scientific meetings and technical advice for the surveillance and clinical trials which are needed, rather than actively implementing research studies. It is anticipated that a technical meeting will review available laboratory techniques, the evidence of circulating colonization factors (CF) in developing countries, and identify gaps in knowledge in basic ETEC science. Consensus is also expected on needs for laboratory-based studies for the next few years, particularly the development of specific laboratory detection methods for the ETEC strains. Surveillance for this disease will be implemented at selected hospitals where studies for rotavirus infection are ongoing. The regional rotavirus networks and selected institutions with the necessary capacity will be used to conduct these studies.

- Weekly Epidemiological Record on ETEC vaccine research meeting is published (early 2006).
- A Collaborating Centre for ETEC research is operational (end 2006).
- A "white paper" on the current status and product development for ETEC vaccine research is generated (end 2006).
- Recommendations on laboratory-based studies and methods for ETEC are available (early 2007).

ROTAVIRUS

In collaboration with PATH and CDC, IVR will continue with the priority areas of rotavirus networks, burden of disease and cost–effectiveness studies, strain characterization, clinical trials in Africa and Asia, and regulatory pathways for rotavirus vaccines.

In addition, new initiatives will focus on post-marketing surveillance in developing countries where the vaccine will be introduced, for which IVR will play a coordinating role. IVR will also actively support work with emerging vaccine producers for the development of upstream rotavirus vaccine candidates.

- Consensus data on global mortality due to rotavirus are available (mid 2006).
- Clinical lots of an upstream vaccine candidate for clinical trials are produced (early 2007).
- A Phase III efficacy study is initiated in Asia with IVR technical and scientific advice (early 2007).
- The rotavirus Phase III vaccine study in Africa is completed (end 2007).

SHIGELLOSIS

IVR will maintain its facilitating role in *Shigella* research with its strategic partners. In addition, it will consider, subject to the availability of resources, establishing

surveillance sites for the burden of disease in various under-studied regions, particularly in Africa. These activities could be coordinated through WHO regional offices and build upon the rotavirus surveillance networks.

Finally, more understanding is needed on the remaining gaps in knowledge, i.e. the correlates of protection and required antigens for vaccine strains; the antibiotic resistance of strains regionally; estimates of the burden of disease attributable to *Shigella*; and the design of vaccine trials in young children in developing countries.

- *Shigella* burden of disease and antibiotic resistance studies are initiated in developing countries (end 2006).
- A "white paper" is published on *Shigella* vaccine product development (mid 2007).
- Consensus is reached on vaccine strain design and correlates of protection (mid 2007).

4.4 *FLAVIVIRUSES*

DENGUE

Work in the coming years will emphasize the importance of clinical evaluation of dengue vaccines, in step with the progress of candidate vaccines sponsored by industry. Relative to this objective, further consultations will be held to identify correlates in conjunction with proof-of-concept clinical trials. Work on the harmonization of assays and provision of standard reagents will also continue. Stakeholder consultations and technical meetings will be convened to provide more detailed guidance to vaccine developers and public health authorities on field evaluation of dengue vaccines. The partnership with PDVI will be strengthened in accordance with these goals.

- Proceedings of the consultation on correlates of protection are disseminated (mid 2006).
- Recommendations are issued on immunological readouts for proof-of-concept and efficacy studies, so that they may be implemented by partners (mid 2007).
- A guidance document on neutralization assays is available (mid 2007).
- Following consultations with all stakeholders, a guidance document is published on field evaluation of dengue vaccines (end 2007).
- Reference and validation reagents are available (end 2007).

JAPANESE ENCEPHALITIS

Work in this biennium will continue to support the accelerated introduction of JE vaccines. As a facilitator, IVR will provide technical advice to interested vaccine developers with advanced candidates that hold promise for public health use. In collaboration with partners, IVR will support strengthening of disease surveillance and diagnostic capabilities in target countries. Technical advice will also be provided for vaccine prequalification and registration by national control authorities, and consultations on immunization strategies organized.

- Vaccine evaluation strategies have been discussed with developing country regulators (end 2006).
- The surveillance standards are field tested in several developing countries and published on the IVR web site (end 2006).
- Diagnostic capabilities are strengthened through dedicated workshops, and countries have started to introduce improved tests (end 2006).
- Country consultations have led to national strategies for the introduction of JE vaccines (end 2007).

- Technical documents on production and control of JE vaccines are updated (end 2007).

4.5 OTHER DISEASES

CERVICAL CANCER (HUMAN PAPILLOMA VIRUS)

IVR will continue its focus on ascertaining acceptability of HPV vaccination through regional and country-level consultations, and facilitating applied research in collaboration with WHO partners responsible for reproductive health, cancer control and adolescent health. It will also provide key input to the Global Immunization Vision and Strategy in helping to design, monitor and evaluate future adolescent vaccination programmes. Work will continue on the establishment of a global HPV laboratory network for effective surveillance and HPV vaccination monitoring through enhanced, state-of-the-art laboratory support. This networking will be instrumental in the dissemination and implementation of HPV standard reagents for quality assurance of laboratory services.

- Standard reagents for HPV DNA and antibody measurements are developed and validated (end 2006).
- Global HPV laboratory network launched (end 2006) and one laboratory per WHO region established (end 2007).
- Global consensus reached on strategies to deliver vaccines to adolescents and young women in the context of strengthening health systems (end 2007).
- WHO on-line database established at the Catalan Institute of Oncology, with information on the estimated burden of cervical cancer, distribution of predominant HPV types in cervical cancer and, where possible, in healthy women for at least three representative countries per region (end 2007).

MENINGOCOCCAL MENINGITIS

In the next biennium, the MVP team will continue its dedicated support to the development of a Men A conjugate vaccine. Focus will go to implementation of the Phase II clinical trials and the establishment of specifications and quality control procedures. The WHO Regional Office for Africa will coordinate the finalization of the strategic plan for Men A conjugate vaccine introduction, including comprehensive communications and resource mobilization plans.

- Phase II clinical trials are performed to demonstrate safety, immunogenicity, and memory of Men A meningococcal conjugate vaccine in the target population (1–29 years) (first pivotal Phase II study to start mid 2006 and second Phase II study by mid 2007).
- Clinical strategy for extension of the indication of Men A conjugate vaccine in infants is developed (end 2006).
- Carriage studies are launched to collect comprehensive data in support of vaccine introduction and roll-out strategies in African meningitis belt countries (early 2007).
- Specifications and quality control procedures of serogroup A conjugate vaccine are completed based on the recommendations established for serogroup C conjugate vaccine (early 2007).

4.6 TECHNOLOGIES AND CROSS-CUTTING PROJECTS

CAPACITY BUILDING IN GOOD CLINICAL PRACTICE (GCP) AND BIOETHICS

IVR will facilitate, coordinate and provide quality assurance for the measles aerosol vaccine Phase II trial in Mexico, sponsored by WHO, the SE36 malaria

vaccine Phase Ib trial in Uganda and the Phase II trial in Indonesia and Uganda, in collaboration with the Osaka University and the Biken Foundation. Post-marketing pneumococcus vaccine trials will be conducted in the Gambia, Kenya and the Philippines.

- Site assessment, GCP training and clinical monitoring are carried out for the Phase II measles aerosol vaccine trial in Mexico (mid 2006).
- Clinical monitoring of the post-marketing pneumococcus vaccine trial in the Gambia and the Philippines is carried out to ensure adherence to ICH-GCP requirements (mid 2006).
- The meningitis polysaccharide vaccine Phase II trial in Ethiopia has adhered strictly to ICH-GCP requirements (end 2006).
- Site assessment and GCP training are completed for trial investigators of the SE36 malaria vaccine Phase Ib trial in Uganda (end 2006), and the Phase II trial in Indonesia (mid 2007).

MEASLES AEROSOL DEVICE COMBINATION

The clinical development plan as well as the regulatory pathway followed is contributing to ensure that the measles vaccine–aerosol device combination will benefit from expedited licensure in India and subsequent pre-qualification by WHO. Activities from the last biennium will continue, and new activities initiated in relation to the Phase II pivotal study in India. The study population will comprise two groups defined by the type of device interface: children between 12 months and 5 years of age will use a face mask, and those over 5 years will use a mouthpiece. The protocol will be planned to satisfy the requirements of a pivotal study in India and thus include the final device configuration(s). Safety data, including on the potential triggering of acute reactive airway disease, wheezing and respiratory distress, will be monitored. The planned duration of follow-up is 12 months.

- Phase I clinical study is completed in India (end 2006).
- Phase II clinical study is completed in Mexico (mid 2007).
- The IND dossier for the Phase II pivotal study is submitted to the Indian Regulatory Authority (mid 2006), the study initiated (end 2006) and the last follow-up visit for trial subjects has taken place (end 2007).
- Consultations are held with experts on the need for and design of a long-term follow-up study to monitor causality between measles aerosol vaccine and asthma (mid 2007).

NEW VACCINE DELIVERY SYSTEMS

IVR will focus on disposable cartridge jet injectors for needle-free immunization. Analysis by the IVR Steering Committee on Novel Vaccine Delivery Systems confirmed that most – if not all – injectable vaccines can be given in this way. Moreover, significant cost-savings might be possible in some cases by using this method to give reduced doses intradermally. Clinical trials will be conducted to evaluate the acceptability and efficacy of normal and reduced-dose delivery, and consensus sought on the regulatory pathway to follow for introduction. Formulations to improve the logistics and efficacy of oral vaccines, particularly in developing countries, will also be pursued as a priority.

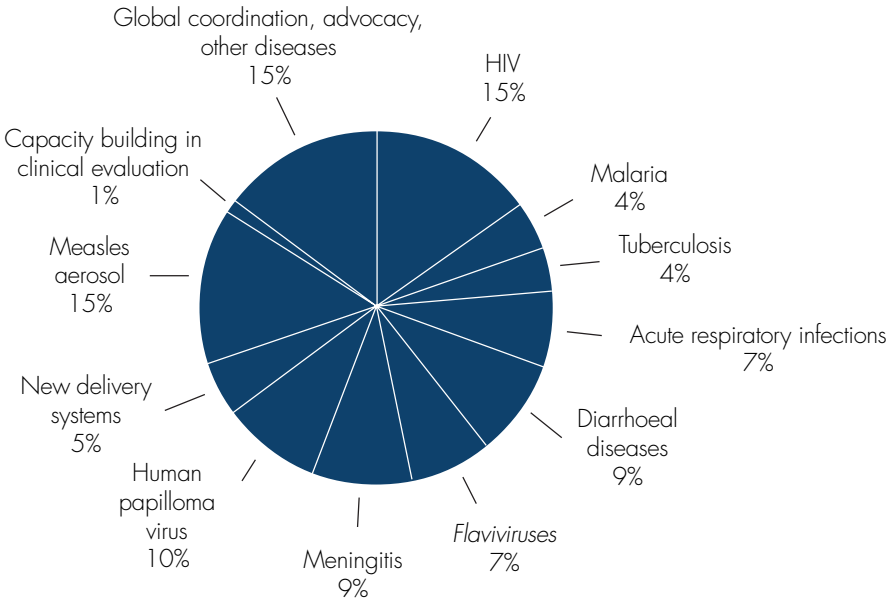
For diseases against which we do not yet have effective vaccines, it is likely that successful vaccine development will require the use of adjuvants to promote potent, rapid and specific immune responses. Public-sector vaccine R&D is hampered by a lack of information on how to

formulate with adjuvants, and limited access to appropriate adjuvants. To streamline the development of future vaccines, IVR will continue to hold annual conferences to facilitate information sharing and to enhance the capacity of national regulatory agencies to evaluate novel vaccines that contain adjuvants.

- A paediatric clinical trial of reduced-dose intradermal delivery of inactivated polio vaccine with disposable cartridge jet injectors is completed (end 2006).
- A clinical trial of reduced-dose intradermal delivery of influenza vaccine with jet injectors is completed (mid 2007).
- International consensus on the regulatory pathway for introduction of jet injectors for vaccine delivery is reached (late 2006).

5. IVR PLANNED EXPENDITURES 2006–2007

Expenditure for the biennium 2006–2007 per disease or theme, as a percentage of the total planned budget of US$ 26.5 million (including regional expenditures).



ANNEX 1: STRATEGIC AREA II OF THE GLOBAL IMMUNIZATION VISION AND STRATEGY

Alarmed that immunization coverage has increased only marginally in some parts of the world since the early 1990s, the heads of WHO and UNICEF crafted a new Global Immunization Vision and Strategy (GIVS) to change this situation by 2015[1]. The World Health Assembly adopted the global strategy in May 2005, which has the following four strategic areas: i) protecting more people in a changing world; ii) introducing new vaccines and technologies; iii) integrating immunization, other health interventions and surveillance in the health systems context; and iv) immunizing in the context of global interdependence.

The Initiative for Vaccine Research is committed to supporting all the goals set out in the document, but clearly has a lead role to play in Strategic Area II, with its three components and activities highlighted below.

STRATEGIC AREA II: INTRODUCING NEW VACCINES AND TECHNOLOGIES

GIVS strategies	Activities
Strategy 8: Strengthen country capacity to determine and set policies and priorities for new vaccines and technologies	▪ Strengthen country capacity to assess disease burden and the cost and cost-effectiveness of new vaccines and technologies through the use of standard tools. ▪ Characterize the optimal product formulations and schedules to maximize impact and minimize cost and operational difficulties. ▪ Assist the country decision-making process, build an evidence base of country experience and methodology at the international level for each new vaccine and technology. ▪ Ensure that the long-term financial requirements from national governments and supporting partners are fully understood and committed to prior to the introduction of new vaccines.

[1] *GIVS: Global Immunization Vision and Strategy 2006–2015*. Geneva, World Health Organization/New York, NY, United Nations Children's Fund, 2005 (WHO/IVB/05.05).

GIVS strategies	Activities
Strategy 9: Ensure effective and sustainable introduction of new vaccines and technologies	▪ Integrate the introduction of each new vaccine into countries' multi-year sector-wide plans and provide a financial analysis. ▪ Ensure adequate training of health workers and vaccine managers at all levels and prepare the logistics and reporting systems. ▪ Produce appropriate information, education and communication materials to ensure good understanding of the benefits of new vaccines or technologies, and their acceptance by parents, communities and health workers. ▪ Ensure that within five years of introduction the coverage of the new vaccine reaches the same level of coverage as for other vaccines given at the same time. ▪ Expand surveillance of diseases that can be prevented by new vaccines, and strengthen laboratory capacity to monitor the impact of these new vaccines on disease patterns and programme operations.
Strategy 10: Promote research and development of vaccines against diseases of public health importance	▪ Produce local evidence to influence and prioritize public and private investments in new vaccines and technologies. ▪ Engage local public health authorities and research communities in defining research agendas relevant to countries which bear a disproportionate share of the disease burden. ▪ Strengthen the capacity of developing countries to undertake the research and development of new vaccines and technologies, including conducting high quality clinical trials and post-licensure evaluations. ▪ Generate geographically and epidemiologically representative clinical data on vaccine effectiveness and conduct demonstration projects of post-licensure evaluations of the impact of vaccination on child survival. ▪ Engage the global research and development community, including vaccine manufacturers, in the design and production of new vaccines against infectious diseases of public health importance, especially in developing countries. ▪ Research and develop evidence-based policies for immunization schedules and strategies as new vaccines and vaccine presentations (e.g., vaccine aerosols) and technologies are introduced.