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The Initiative for Vaccine Research
Report 2004–2005

Department of Immunization, Vaccines and Biologicals

The Initiative for Vaccine Research

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Copies may be requested from:
World Health Organization
Department of Immunization, Vaccines and Biologicals
1211 Geneva 27, Switzerland
Fax: +41 22 791 4227 e-mail: vaccines@who.int
Ordering code: WHO/IVB/06.05

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Introduction

At the start of the 2004–2005 biennium, the Initiative for Vaccine Research (IVR) pledged to use its unique strategic position to promote a global and sustainable research and development (R&D) pipeline delivering optimal vaccines for priority diseases, especially in developing countries. This report looks at the progress made towards this undertaking, and shows how experience gained over the last two years has shaped the direction IVR will take over the next two bienniums.

RECENT SUCCESSES AND CHALLENGES IN VACCINE RESEARCH

It is well-known that the time from discovery to delivery of a new vaccine can take more than a decade. During this process, candidate vaccines must overcome numerous scientific, financial, technical and regulatory hurdles if they are to become the live-saving interventions we need. Furthermore, this process "or pipeline" must be regularly injected with new antigens to guarantee that one will finally reach the market. This is an extremely costly affair: a single, successful vaccine can cost anything up to US$800 million, not counting the investment needed for its introduction and post-market monitoring[1]. It is no wonder that many developing countries, stretched to devote US$25 per capita on their total health expenditure[2], cannot afford new vaccines. Encouragingly, the last biennium saw a tremendous increase in commitment, revenues and R&D which will accelerate the passage of new and improved products through the global vaccine pipeline. Indeed, it is currently estimated that the number of available vaccines will double over the next 10–15 years to around 40.

Highlights of recent vaccine R&D successes globally include:

- Two rotavirus diarrhoea vaccines, one licensed in Europe and the other in the United States of America (USA), as well as in a number of developing and middle-income countries;
- A tetravalent meningococcal meningitis vaccine licensed in the USA;
- A nine-valent pneumococcal conjugate vaccine that showed 16% protection against overall child mortality in the Gambia;
- Bivalent and tetravalent human papillomavirus vaccines protecting against cervical cancer;
- A malaria vaccine that showed 58% protection against severe disease in a Phase II clinical trial in Mozambique; and
- A live attenuated vaccine for Japanese encephalitis that will soon be deployed in India and other disease-endemic countries.

Challenges for vaccine R&D have included the need to respond rapidly to new threats such as Severe Acute Respiratory Syndrome (SARS) and more recently avian

influenza, notably the ability to scale up vaccine manufacturing capacity in response to pandemics. Developing countries, where population density is high and medical treatment suboptimal, are particularly vulnerable to these threats. IVR responded swiftly in 2004 and 2005 to the avian influenza pandemic by promoting the development of a new generation of influenza vaccines that induce broad spectrum and long-lasting immune responses and provide protection against different influenza viruses.

Opportunities have included improved disease surveillance and the evidence base to promote R&D, and working *with* developing countries at all levels of vaccine research. For IVR, this means testing candidate vaccines in clinical trial sites where the disease is endemic; it means strengthening national capacity to carry out all aspects of research; and it means drastically reducing the unethical time lag between introduction of the vaccine in resource-rich countries, and in disadvantaged nations. In 2004–2005, IVR expanded regional networks for the surveillance of rotavirus disease burden; supported clinical studies in numerous developing countries; and carried out training in bioethics, Good Clinical Practice, regulatory systems and laboratory functions for researchers and institutions, particularly in Africa, Asia and Latin America.

We can be satisfied with the progress that has been made. Despite this, a number of priority diseases "such as enteric and tropical diseases, and various viral and bacterial respiratory infections" still lack strong leadership, partnerships, funding and supportive implementation research to bring a vaccine to market. Mitigating these challenges and maximizing these opportunities have been at the centre of IVR activities.

ROLE AND MISSION OF IVR

"Accelerate innovation for the development and optimal use of safe and effective vaccines and technologies against infectious diseases of public health importance"

It is easy to think of vaccine research as product development, and IVR plays a key role to support this where it has a comparative advantage. Yet in order to reach the above goal, studies are also needed to introduce a vaccine or technology once it has been registered, in different areas of the world, and in population groups with different age, gender and ethnic make-up. The safety, efficacy and public health impact of the vaccine still need to be monitored in use, and any obstacles overcome

with research into an improved vaccine. IVR therefore carries out *implementation research* that, together with *product research and development*, address the wide range of issues all along the vaccine pipeline and beyond.

IVR's role in vaccine R&D is either as a developer or a facilitator, depending on the public health gap that needs to be filled at any given time. The box below provides examples of these two types of support.

DEVELOPER AND FACILITATOR

IVR acts as a *Developer* when a candidate vaccine lacks R&D investment and leadership, and where an active role in product development will benefit the vaccine pipeline for the disease in question. In such cases, IVR dedicates human and financial resources to specific projects, and combines its strengths with those of other "developers" by assuming certain tasks or co-sponsoring others. The Measles Aerosol Vaccine is an IVR Developer project.

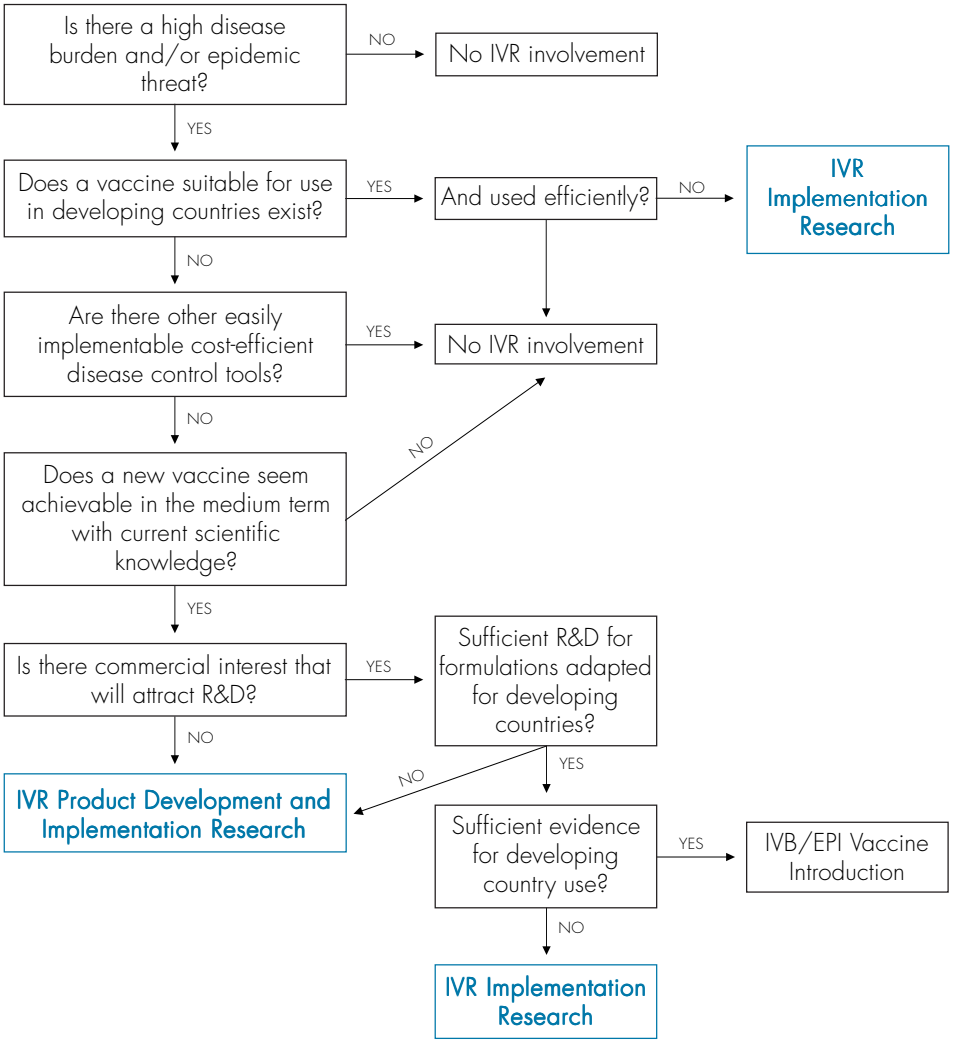
IVR fulfils a *Facilitator* role for priority diseases such as AIDS, tuberculosis or dengue, where there are many funding agencies and product development programmes already active in the vaccine R&D pipeline. In these cases, IVR acts as an independent, objective, process consultant and strategic or technical adviser. Generating an enabling environment for human papillomavirus vaccine development and global introduction is an IVR Facilitator project.

PRIORITIZATION PROCESS

Limited funding is not the only criterion for a decision on whether to invest in a vaccine against an infectious disease. Much before this filter, IVR carries out a prioritization process that starts with the prerequisite that the disease is of public health importance, continues with a review of alternative disease control tools, and ends with a decision on the extent and type of IVR involvement. Figure 1 illustrates this process.

The coordination role of IVR in bringing vaccine research efforts together under one roof has thus proved invaluable in alleviating overlap and creating better synergies among colleagues and partners.

FIGURE 1. IVR PRIORITIZATION PROCESS



PARTNERSHIPS

During the last biennium, IVR continued to work closely with existing partners and forged new ones to achieve common goals. IVR's closest "partners" are in its immediate vicinity in the WHO Department of Immunization, Vaccines and Biologicals, where it benefits from expertise in quality assessment, regulatory affairs and systems strengthening. As a WHO entity, IVR also benefits from close proximity to the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and a sister agency, the Joint United Nations Programme on HIV/AIDS (UNAIDS), among others.

Significant strides forward have been made by the African AIDS Vaccine Programme, a WHO-UNAIDS supported consortium of African scientists seeking to accelerate the discovery of safe, affordable and accessible HIV vaccines for Africa. Other successful partnerships include the WHO-PATH Meningitis Vaccine Project, which is pioneering the development of a low-cost conjugate *Neisseria meningitidis* serogroup A vaccine for Africa and the GAVI Accelerated Development and Introduction Plans.

The annual Global Vaccine Research Forum met in June 2004 and 2005 and brought all partners together "over 200 of the world's top vaccine scientists" to present state-of-the-art research and find solutions to challenges, especially those facing developing countries. A keynote address was presented at the last Forum on the indispensable role of public–private partnerships in vaccine research. IVR specifically works with such partnerships to facilitate clinical and/or laboratory standards and protocols; strengthen developing country capacity in the areas of bioethics, regulation and Good Clinical Practice; and conduct research on future access (cost-effectiveness studies, introduction plans, national decision-making support tools).

IVR REGIONAL COLLEAGUES

The last biennium has witnessed the reinforcement of WHO regional office involvement in vaccine research. This trend towards decentralization, which will gather momentum in the coming years, aims to ensure that support is more directly accessible for governments and research institutions in developing countries. To date, the WHO regional offices for Africa, the Americas and South-East Asia have become operational, and it is hoped that further offices will follow suit as soon as feasible. The box below is an example of an activity carried out under the auspices of IVR regional colleagues.

RUBELLA: A VACCINE-RELATED RESEARCH PRIORITY OF THE PAN AMERICAN HEALTH ORGANIZATION

Vaccine-related priorities for the Pan American Health Organization (PAHO) include the elimination of rubella and congenital rubella syndrome; sustaining progress in measles elimination and polio eradication; strengthening information management; and introducing new and underutilized vaccines. Research studies on rubella were conducted in Brazil, Costa Rica, Ecuador and El Salvador and to determine the potential adverse effects in neonates of mothers inadvertently vaccinated with rubella vaccine during pregnancy. The study aimed to establish the immune status of the mother, the presence or absence of congenital rubella infection or anomalies in the newborn and to determine whether a rubella IgM positive status in neonates was attributable to vaccination of the mother. The results of the Ecuador study showed that of nearly 2.5 million women vaccinated against rubella, 1,291 pregnant women were inadvertently vaccinated. The final diagnosis after follow-up of those satisfying the inclusion criteria showed that the two infants who presented a pathology were actually suffering from congenital cytomegalovirus (CMV) infection, and not from adverse effects of their mother's rubella vaccination. The researchers, all Ecuador nationals, learnt:

- the need for a well-defined protocol that is discussed in detail with all stakeholders, particularly mothers and families, paediatricians, and maternity hospital staff;
- the importance of training for all staff involved, e.g. to ensure complete and accurate data collection and the appropriate timing of specimen collection;
- the need to provide mothers and their families with sound and relevant advice.

PAHO is also a co-investigator with the US Centers for Disease Control and Prevention on a research project entitled "Diagnosis and Molecular Characterization of Rubella by Using Filter Paper Dried Blood Spots and Oral Fluid". The overall objective of the project in Peru is to determine whether dried blood spots and oral fluid-based assays for the detection of rubella-specific IgM and IgG are feasible alternatives to laboratory confirmation of rubella.

WHO AND HEALTH RESEARCH

In response to resolution WHA58.34 on the Ministerial Summit on Health Research, IVR contributed to a position paper describing WHO's role and responsibilities in health research[3]. This paper, presented to the WHO Executive Board in January 2006, was based in part on an initial assessment on this issue carried out in June-July 2005. As a purely research-focused initiative, IVR was a top informant of the survey and its recommendations. It was agreed that WHO's primary responsibility is to lead by example, using best practices in applying the results of research to inform policy, practice and public opinion. WHO is also tasked to ensure that all research carried out meets the highest standards of ethics, that research capacity is strengthened at national level, and that access to information on research projects is improved.

"Improvements in health are essential if progress is to be made with the other Millennium Development Goals"

Dr LEE Jong-wook
WHO Director-General

IVR took this opportunity to establish a database of all vaccine research activities carried out under its auspices (see Annex 2 for a breakdown of vaccine research projects during 2004–2005). A preliminary review of the data showed that, discounting advocacy for vaccine R&D, the highest number of projects focused on rotavirus, HIV and pneumococcal vaccines, while rabies, *Shigella* and rubella featured at the lower end of the scale. The majority of studies were carried out in the African region, and on product R&D. More than half were investigator initiated. IVR intends to publish the data at regular intervals in the future.

RABIES: A SMALLER IVR CASE STUDY

The need to replace rabies immune globulin (RIG) as an essential component of rabies post-exposure prophylaxis is widely acknowledged. The objective of this project was to identify a unique combination of murine anti-G monoclonal antibodies (MAbs) from available MAb panels at WHO Collaborating Centres for Rabies able to replace RIG. The ultimate goal is to make a product which can be used broadly in developing countries at the lowest reasonable price to the public sector of these countries.

The first phase of this project should lead, after careful selection of candidate MAbs, to the evaluation and validation in vitro and in vivo of the efficacy of the MAbs cocktail for rabies prophylaxis in combination with vaccination. The second phase should lead to the selection of a technology for production by manufacturers in developing countries.

LONG-TERM RESULTS

Given that a vaccine can take over 10 years from synthesis to market, strategies, plans and progress need to have the same time frame. In line with other WHO policy documents, the new IVR Strategic Plan spans more than one biennium. In fact, IVR is looking 10 years ahead to meet the goals of the Global Immunization Vision and Strategy (2006-2015)[4]. IVR was instrumental in shaping the vision, goals and approaches of this new strategy, and particularly for Strategic Area II "Introducing New Vaccines and Technologies". With an unprecedented number of new or improved vaccines expected to become available over the next fifteen years, IVR outlines in the GIVS document how it aims to provide developing countries with the tools they need to make rational decisions when faced with a bewildering choice of which vaccines to introduce into their national

immunization programmes. Another important strategy in the introduction of new vaccines and technology component of the GIVS vision is to ensure that R&D into future vaccines against diseases of public health importance is promoted, and that the fruits of this R&D are made available, especially to disadvantaged populations with a high burden of disease.

IVR will also embrace the health-related goals, targets and indicators of the United Nations Millennium Development Goals. Reducing child mortality rates by two thirds (Goal 4), combating HIV/AIDS, malaria and other diseases (Goal 6), and forging global partnership to ensure access to medicines (Goal 8), will be significantly easier to achieve with accelerated vaccine R&D.

DOCUMENT OUTLINE

This document shows progress over last two years towards IVR's long-term vision and mission outlined above, presented through activities to achieve a set of pre-established milestones. Sixteen sections discuss: HIV/AIDS, malaria, tuberculosis, acute respiratory infections, diarrhoeal diseases, *flaviviruses*, human papillomavirus, meningitis, and three technology and capacity-building projects. Each section presents an overview of the relevant global issues before introducing the activities, successes and challenges encountered. A simple scoring system notes whether progress has been significant (✓) or whether the activity has been delayed or reprogrammed (←). Of the 85 milestones set for the development of vaccines and technologies against these diseases, 72 (85%) were fully or mostly achieved. Each section ends with brief projections for the 2006–2007 biennium[5].

The report ends with a series of annexes presenting for the period 2004–2005: a summary of IVR expenditure, a breakdown of IVR research projects by disease or technology, an inventory of IVR scientific publications and a list of the IVR steering committees and advisory bodies.

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5 See IVR Strategic Plan 2006-2009, www.who.int/vaccine_research/documents/.

HIV/AIDS vaccines

FOCUS

Since the start of the HIV pandemic, more than 25 million people have died of AIDS. The number of people living with HIV has reached its highest level ever: an estimated 40.3 million. Close to five million people were newly infected with the virus in 2005. The development of a safe, globally effective and affordable HIV vaccine will constitute an important complement to existing HIV prevention, treatment and care strategies, especially for vulnerable populations and resource-limited countries.

Since the first HIV vaccine trial in 1987, over 50 candidates and "prime-boost" combinations have been tested in multiple clinical trials, including two Phase III trials, in developed and developing countries. The results from these trials show that although most candidate vaccines are safe, their immunogenicity is rather weak and short-lived. The quality of vaccine-induced antibody responses has been limited to laboratory-adapted HIV strains. The high genetic diversity of HIV strains continues to pose a major challenge for HIV vaccine development, especially in Africa. In the absence of solid scientific knowledge of mechanisms of immune protection against HIV, parallel vaccine strategies are being explored, which will require the establishment of multiple vaccine trial sites.

Role of IVR

The mission of the WHO-UNAIDS HIV Vaccine Initiative (HVI) is to promote the develop-ment, evaluation and future availability and public health use of HIV vaccines with a focus on the needs of developing countries. HVI primarily acts as a facilitator and "neutral broker". Activities also include advocacy, guidance and coordination of international HIV vaccine efforts; and capacity building to conduct clinical trials of promising candidate vac-cines at the highest scientific and ethical standards. These activities are in line with and comple-mentary to the goals and objectives of the Global HIV Vaccine Enterprise.[1]

Overview 2004–2005

In addition to the activities described below, WHO actively supported the development of the African AIDS Vaccine Programme (AAVP), whose primary objective is to promote HIV vaccines through capacity building and strengthening clinical trial infrastructures in preparation for all phases of trials in Africa. A series of training workshops, capacity build-ing projects and National AIDS Vaccine Plans were supported by AAVP. The AAVP framework was used as a template to encourage similar networks in all regions for developing countries to support HIV vaccine development.[2]

Reaching 2004–2005 milestones*

✓ **HVI advocacy strategy**
The three major elements of the Global HIV Vaccine Advocacy Strategy are Policy, Strategic Planning and Future Access, each of which was developed through detailed discussions with all Global Partners.[3] The AIDS Vaccine Handbook: Global Perspectives was co-funded by HVI through the AIDS Vaccine Advocacy Coalition.[4]

✓ **HVI and the Global HIV Vaccine Enterprise**
HVI contributed to the Scientific Strategic Plan of the Global HIV Vaccine Enterprise by co-organizing and participating in working groups, and providing technical advice on regulatory aspects and clinical trials site development[5]. The 3rd African AIDS Vaccine Programme Forum[6] was co-sponsored by the Enterprise along with multiple other international partners. A consultation process is under way to formalize cooperation between HVI and the Enterprise.

✓ **New Phase III trials in industrialized and developing countries**
In 2004, recruitment for a third Phase III trial started at 40 different sites in south-eastern Thailand with a prime boost combination. This is a large-scale, population-based trial of 16 000 volunteers, who had all received their first vaccination dose

* ✓= largely achieved ← = delayed or reprogrammed

by the end of 2005. HVI has contributed to this success through financial and technical support to the Thai National AIDS Vaccine Plan, by reviewing the protocol and by supporting various consensus-building community workshops in preparation for the trial.

In 2005, a multi-centred, proof-of-concept Phase IIb trial with an Adeno5 candidate vaccine was launched. HVI provided technical advice and a detailed review of the protocol, addressed ethical and regulatory aspects of large-scale trials (notably policies and strategies to ensure access to care and treatment), and contributed to strengthening regulatory capacity and normative frameworks.

✓ HIV vaccine candidate Phase I/II trials in developing countries

Phase I/II vaccine clinical trials were initiated in 11 developing countries (Botswana, Brazil, the People's Republic of China, Haiti, India, Kenya, Peru, Rwanda, South Africa, Uganda and the United Republic of Tanzania). IVR facilitated the preparation of these trials by providing: technical advice and protocol review by the WHO-UNAIDS Vaccine Advisory Committee; support to the National AIDS Vaccine Plans; training and capacity building to meet Good Clinical Practice and Good Laboratory Practice standards; and by implementing activities relative to the AAVP workplan. The training workshops for the latter activity were carried out with strategic partners using the AAVP regional networks in several countries, including Ethiopia, Senegal, South Africa, Thailand and the United Republic of Tanzania.

✓ A credible estimation of demand for and access to future HIV vaccines

To avoid delayed or ineffective access to future HIV vaccines, HVI facilitates global and national policy work on the delivery and cost–effectiveness of potential vaccines. A scientific article providing full details and the methodology used for this project was published in *AIDS* in September 2005.[7]

An international collaborative research project was established in Brazil, China, Kenya, Peru and Thailand to explore public health perspectives for access and development of vaccination strategies for future HIV vaccines. These countries were chosen for their epidemic pattern and their engagement in HIV vaccine trials. The pro-gress made and results generated from the studies in Brazil, Kenya and Thailand were pre-sented and discussed at technical consultations.[8] The study is designed in three parts: (i) a survey to assess challenges and opportunities for country-level capacity to deliver potential HIV vaccines; (ii) the collection of cost data associated with HIV vaccination and AIDS treatment; and (iii) a modelling exercise analysing the relative cost–effectiveness of poten-tial HIV vaccination strategies, including the development of training tools for effective application of country-specific models by public health experts in developing countries.

✓ **Gender, age, and ethnicity in HIV vaccine-related research and clinical trials**

The increasing proportion of women among adults living with HIV in all regions of the world led IVR to host a consultation in August 2004 on issues related to gender, age and ethnicity in HIV vaccine research and clinical trial recruitment. Recommendations covered general research issues, ethics and conduct of clinical trials, advocacy and community participation and policy. IVR was tasked to: devise user-friendly and culturally appropriate guidance for informed consent; strengthen the capacity of national ethics committees; update WHO/UNAIDS guidelines for ethical conduct of HIV/AIDS vaccine trials; and propose better ways to carry out research, handle gender issues and the enrolment of women and adolescents in HIV vaccine trials.[9]

2006–2007

HVI will maintain its role as facilitator and impartial broker in support of global efforts to promote HIV vaccine research and development, 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 coun-tries; and guidelines to assess the cost–effectiveness of HIV vaccination strategies for public health use.

2006–2007 milestones

- 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).

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HIV Vaccines Contacts

Dr Saladin Osmanov, Coordinator

Dr Raymond Hutubessy, Health Economist

Mrs Coumba Touré, Technical Officer

Dr Madani B. Thiam, Technical Officer, WHO Regional Office for Africa

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Malaria vaccines

FOCUS

Malaria is by far the world's most deadly tropical parasitic disease, killing more people than any other communicable disease except AIDS and tuberculosis. Worldwide prevalence of the disease is in the order of 350–500 million clinical cases each year, with an estimated annual death toll of over 1.1 million. The vast majority of deaths occur among children under five years of age, especially in remote rural areas with poor access to health services. The emergence and resurgence of malaria continues in over 100 endemic countries across the globe, largely due to drug-resistant parasites and insecticide-resistant vectors. The development of a safe, effective and affordable malaria vaccine is therefore a global public health priority.

A Phase IIb clinical trial of the most advanced candidate malaria vaccine, RTS,S/AS02A, has been completed in 1-4 year old children in Mozambique. The vaccine appeared safe, was well tolerated and demonstrated preliminary efficacy of 30% against clinical disease and 58% against severe malaria. Results from follow-up studies showed evidence that this protection can last at least 18 months.[1-2]

Role of IVR

IVR facilitates and coordinates the development of malaria vaccines among public and private groups. This role is critical to reduce fragmentation and duplication of activities, as well as to identify gaps and encourage research into neglected areas. For example, IVR coordinates an informal group of malaria vaccine funding agencies that identifies common strategic priorities and carries out activities in synergy. In its normative functions, IVR supports the preclinical and clinical evaluation of candidate vaccines.

Overview 2004–2005

The management of science and information included improving and maintaining the global portfolio of candidate vaccines on the IVR web site. IVR was invited to increase its involvement in the preclinical development and clinical testing of specific vaccine candidates, and in developing a strategy to ensure the standardization of useful assays. Lower priority was thus given to work on improved correlates of protective immunity and on a Phase IIa standard model protocol for malaria vaccine efficacy trials. Progress towards technical and normative guidance on how to evaluate malaria vaccines was also made at expert group consultations.

Reaching 2004–2005 milestones*

✓ **Animal and primate models to screen candidate malaria vaccine antigens**
A thorough review and critical analysis on the use of animal models in the malaria vaccine development field was carried out as a prelude to standardization of primate models. Given the multiple candidate vaccines in development, IVR's normative functions and its coordination of an expert forum to address the many issues related to their evaluation were perceived as vital.[3]

✓ **Immune assay development**
A working group on Malaria Vaccine Laboratory Assays was established to review assay development, optimization, validation and standardization. The first meeting of the working group concentrated on humoral, functional and cellular assays with the aim of standardizing and validating assays from Phase I through to Phase III trials.[4] IVR will coordinate the work of the group in standardizing potential immune correlates or surrogate markers of protection.

✓ **Upgrading a malaria vaccine clinical trial site to meet Good Clinical Practice (GCP) and the PfCP-2.9 Phase I/II trials**
IVR worked with the Changhai Hospital in Shanghai, People's Republic of China to ensure its capacity to conduct trials to GCP standards. The IVR-sponsored *Plasmodium falciparum* chimeric protein (PfCP-2.9) Phase I clinical trial at the site was thus successfully completed. Preliminary results showed the vaccine to be safe and immunogenic, despite technical difficulties with analyses of the

* ✓= largely achieved ← = delayed or reprogrammed

functionality of the vaccine-induced antibodies by growth inhibition assay. The results of this study will be published in 2006.

The development of PfCP-2.9 continues in collaboration with the Malaria Vaccine Initiative and Wanxing Biopharmaceuticals. Trends in the immune response from the first trial indicated that it was not enhanced by increasing dosage levels. A new batch of the vaccine meeting current Good Manufacturing Practice will be tested to explore the effects of spacing out the vaccine schedule as well as lowering the dosage levels. The trial is expected to begin in early 2006. IVR will continue to provide GCP and ethics training for clinical trials of the vaccine, and take responsibility for the safety monitoring.

✓ **Increased focus on the preclinical development and clinical evaluation of malaria vaccines**

Following a technical meeting to discuss Phase IIb efficacy endpoints, it was agreed that a major priority for IVR should be the standardization of clinical evaluation of malaria vaccines. An international collaborative working group was therefore set up to address, inter alia:

- the study design of efficacy trials and analytical methods;
- standardization of study methodology and trial specimen collection methods, including the frequency, timing and duration of sampling;
- the sharing of clinical development plans, laboratory and trial results and assistance in the conduct of trial-related activities.

The working group will also ensure consensus on definitions of malaria disease for vaccine trials.

← **Global portfolio of candidate malaria vaccines**

Rather than a registry of trial sites by region and capacity, priority was given to information and knowledge on the global portfolio of candidate malaria vaccines, their stage of development and their sponsors. This portfolio will be updated regularly and is available on the IVR website.[5]

✓ **Minimum criteria for a site to conduct malaria vaccine trials**

IVR facilitated the development of a questionnaire for use by WHO or on-site personnel to evaluate whether minimum criteria have been met to carry out a malaria vaccine trial. The questionnaire can also be modified for use in any other vaccine trial.

2006–2007

IVR remains committed to providing technical support for research and development 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.

Milestones 2006–2007

- 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 endpoints 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).

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Malaria Vaccines Contacts

Dr Zarifah Reed, Scientist

- www.who.int/vaccine_research/diseases/soa_parasitic/en/index4.html
- www.who.int/topics/malaria/en/

Tuberculosis vaccines

FOCUS

Around two billion people "or one-third of humanity" are currently infected with tuberculosis (TB), the vast majority of whom live in developing countries. This situation led WHO to declare TB a global emergency in 1993, yet 12 years later we are witnessing a 2% rise in the number of cases every year. The AIDS pandemic is a major 'amplifier' of the TB crisis. The 'Global Plan to Stop TB' underlines the urgency to develop new and more effective TB vaccines as a complement to existing strategies to control the disease, particularly for parts of Africa and Eastern Europe. Fortunately, this has started to gain significant momentum: encouraging and consistent scientific results from the laboratory and from early field trials indicate that new effective TB vaccines may be introduced within the next 10 years. Today, six TB vaccine candidates are in Phase I or II trials. New vaccines to prevent childhood and adult forms of tuberculosis, to alleviate existing infections, or to shorten drug treatment regimens, will fundamentally alter our approach to TB control.

Role of IVR

The WHO Steering Committee on New TB Vaccines recommends actions to bridge the gaps in the development and introduction of improved prophylactic TB vaccines in countries with the highest burden of disease. Recommendations relate to information needs, consensus-building in the preclinical and clinical evaluation of vaccines, economic analyses, harmonization of norms and pre-introduction activities.

Overview 2004–2005

During 2004–2005, IVR concentrated on normative work and capacity strengthening for preclinical and clinical development of new TB vaccines. In the same period, the first TB vaccine candidates progressed from preclinical development to clinical evaluation in human beings. Supplementary activities, such as information and economic analyses for endemic country audiences, covered the pre-introduction and later stages of development. The gold standard reference vaccine and challenge strain of *M. tuberculosis*, developed with funding from IVR, is now being distributed by the US Food and Drug Administration to all laboratories working on TB clinical development.

A significant achievement has been the integration of the TB vaccine community into mainstream TB research and control through a vaccine working group 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 tuberculosis as a public health problem. IVR prepared the vaccine section of the Global Plan to Stop TB: 2006-2015[1]. Another noteworthy achievement has been consensus from the broad TB vaccine community for taking BCG-based live attenuated microbacteria into clinical trials.

Reaching 2004–2005 milestones*

✓ Animal models

Standard protocols for all common animal models used to evaluate TB vaccine efficacy and safety were published on the TB vaccine website.[2]

← Health economics study

The outline of the health economics study prepared in collaboration with the Stop TB Partnership was put on hold until parameters such as target product profiles, introduction date and vaccine price become clearer. Smaller, cost–effectiveness studies will therefore commence in 2006.

✓ Standardized immune assays

Consensus was reached on standardized immune assays to be used as endpoints in Phase II trials of TB vaccine.[3] These include a whole blood and an ELISPOT

* ✓= largely achieved ← = delayed or reprogrammed

assay for measuring the induction of Interferon-gamma, as well as multi-parameter FACS-scan analysis.

✓ **Guidelines for clinical investigation**
Generic guidance documents on Phase I and II vaccine trials were published, and a Phase III trials sites directory initiated. The latter will be integrated into the generic clinical vaccine trial site database being finalized by IVR.[4]

✓ **Capacity building for Phase III efficacy testing**
Only one site is ready to start Phase III trials of a new TB vaccine (Western Cape province, South Africa), since it proved difficult to identify sites that combine laboratory capacity with the epidemiological profile required. It is expected that by 2008–09, when efficacy trials should begin, several other sites will be available in Africa and Asia. IVR will continue to provide training, and a forum for consensus-building on protocol design for Phase III trials.

✓ **Guidelines for BCG characterization**
IVR worked on the standardization and molecular characterization of BCG in collaboration with the WHO Quality, Safety and Standards team, since the existing TB vaccine will most certainly form part of any new vaccine along with other antigens in one form or another.[5-6]

✓ **Phase I/II clinical trials of candidate vaccines**
Four Phase I trials of TB vaccine candidates and two Phase II trials were successfully completed. IVR facilitated consensus building, strengthened capacity and fulfilled its normative functions.[7]

✓ **TB vaccine research on the Internet**
In collaboration with the Global Stop TB Partnership, a web site was launched that provides information on the state of the art of TB vaccine development, including vaccine candidates, BCG, clinical trials and regulatory aspects.[8]

✓ **TB vaccine impact model**
A mathematical algorithm is available through the WHO/TB web site that models the impact that new TB vaccines with user-definable product profiles will have when introduced into selected high-burden countries.This algorithm can be customized.

2006–2007

The next 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 endpoints, 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.

Milestones 2006–2007

- A resource and training centre for the evaluation of immunological endpoints in TB vaccine trials is established (end 2006).
- Consensus on standard clinical endpoints 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).

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Tuberculosis Vaccines Contacts

Dr M. Teresa Aguado, Coordinator

Dr Uli Fruth, Scientist

- www.who.int/vaccine_research/diseases/tb/en/
- www.who.int/topics/tuberculosis/en/

Influenza vaccines

FOCUS

Each year, influenza epidemics kill up to one million people, making it a major public health threat worldwide. Current inactivated vaccines have disadvantages such as reduced immunity in the elderly and young children. Moreover, a new vaccine is needed almost every year to ensure that the strains match antigenic changes in the circulating wild viruses. In view of this, new influenza vaccines that are more immunogenic and cross-protective will offer significant advantages, including being effective in developing countries. Facilitating the development of such vaccines is therefore a WHO priority, although this may take several years. Meanwhile, the looming risk of a pandemic, with H5N1 avian influenza as the potential cause, has made the accelerated development and evaluation of prototype H5N1 vaccines an imperative.

Role of IVR

In 2004, IVR established a project to promote the development of a new generation of influenza vaccines that induce broad spectrum and long-lasting immune responses and provide protection against different influenza viruses. IVR provides a forum for coordination of international efforts to develop new vaccines, standardize immunological assays and evaluate vaccines in clinical trials. IVR coordinates a similar international forum for the review, development and evaluation of vaccines for pandemic influenza.

Overview 2004–2005

Several meetings reviewed the development of a new generation of influenza vaccines, from which a research agenda was developed and recommendations made for WHO action. The role of different components of the immune system in protecting against influenza infection was evaluated and potential correlates of protection assessed. IVR, together with the WHO Global Influenza Programme, overviewed the current status of preclinical development clinical evaluation of H5N1 and H9N2 pilot pandemic vaccines. Three reports were submitted for publication in leading journals.[1-3]

Reaching 2004–2005 milestones*

✓ Research priorities for new generation influenza vaccines[1]

An expert consultation identified the following research priorities:

- Expand understanding of how a vaccine can induce protection against distinct influenza viruses through stimulation of different components of the immune system;
- Evaluate progress in research and development;
- Conduct clinical trials towards the development of novel influenza vaccines using conserved viral proteins; and
- Evaluate mucosal delivery of vaccines and use of adjuvants to enhance vaccine-induced immune responses.

✓ Development and evaluation of pandemic influenza vaccines in preclinical and clinical trials[2]

Experimental lots of vaccine using strains provided by WHO or WHO Collaborating Centres were produced and evaluated in animals by several manufacturers of influenza vaccines, and three producers initiated clinical trials. Discussion with influenza vaccine producers and national regulatory authorities focused on information exchange and projections of a time-line for demonstration projects to develop and evaluate H5N1 and N9N2 vaccines. The latest status of

* ✓= largely achieved ← = delayed or reprogrammed

development and evaluation of pilot pandemic vaccine lots was assessed at a consultation held in November 2005. Preliminary results suggest that H5N1 and H9N2 vaccines are safe, well tolerated and immunogenic. Vaccines with a low antigen content appear immunogenic if a potent adjuvant is included in the final formulation. The presence of adjuvant increases the cross-reactivity of vaccine-induced antibodies against different subtypes of influenza viruses.

✓ **Immunological assays as indicators of influenza vaccine immunogenicity and efficacy[3]**

Participants at WHO expert meetings analysed the current status of standardization of immunological assays and reagents and available data on the role of antibodies and T-cell immune responses in protection against influenza viruses. Standardization of neutralization assays was recommended since they were considered the best indicator of vaccine efficacy. Considerable progress was also made on standardized immunological assays to measure T-cell immune responses.

✓ **Standardization of microneutralization assay for influenza virus**

Standardization of a neutralization test for influenza virus was initiated. The method is based on an ELISA-based microneutralization format. The first stage of the international collaborative study was completed with the participation of 18 laboratories from five countries, and the results are being analysed. A standardized protocol for the microneutralization assay will be available during 2006.

2006–2007

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.

Milestones 2006–2007

- 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).

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Influenza Vaccines Contacts

Dr Klaus Stohr, Senior Advisor, Pandemic Influenza Vaccines

- www.who.int/vaccine_research/diseases/ari/en/ f& www.who.int/topics/influenza/en/

Pneumococcal vaccines

FOCUS

Pneumococcal disease is considered to be a leading cause of childhood morbidity globally and childhood mortality in developing countries. However, the true burden of disease is difficult to determine since methods for establishing pneumococcal etiology of pneumonia "the commonest syndrome caused by this organism" are insensitive. Burden statistics, therefore, have to be estimated indirectly using mathematical models.

Available data suggest that pneumococcal conjugate vaccines are safe and effective. However, progress with introduction of the vaccine in developing countries has been constrained by insufficient data on the burden of disease and serotype distribution in these countries, inadequate supply and high prices. The supply of 7-valent vaccines has improved, and formulations with even higher valencies should become available in the coming years.

Role of IVR

IVR's role is to promote the development of pneumococcal vaccines appropriate for developing country settings, to evaluate alternative immunization schedules, and to assist Member States to generate data to make informed decisions about vaccine introduction, and optimal vaccination schedules, for their immunization programmes.

Overview 2004–2005

IVR has been leading an effort to generate or update global, regional and national pneumococcal disease burden estimates, based on best available data. In collaboration with partners, notably the Pneumococcal Accelerated Development and Introduction Plan (PneumoADIP) of the Global Alliance on Vaccines and Immunization, IVR established surveillance networks in Africa and Asia and is developing generic tools aimed at improving estimates of pneumococcal disease burden and the serotype distribution of the organism in regions and subregions where data are inadequate.

Clinical trials were supported to demonstrate the efficacy and effectiveness of pneumococcal conjugate vaccines, including trials of alternative vaccination schedules, in developing country populations.

IVR worked closely with the WHO Department of Immunization, Vaccines and Biologicals to: (i) establish reference laboratories for the standardization of immunological assays, and reference reagents and standards to facilitate assessment of new vaccine candidates; and (ii) define regulatory pathways for pneumococcal vaccines at the clinical stage.

Reaching 2004–2005 milestones*

✓ Networks for laboratory-confirmed pneumococcal disease in developing countries

The surveillance networks for laboratory-confirmed pneumococcal disease, established to cover 10 countries in East Africa and South-East Asia, are generating valuable information. Proposals for regional networks in the Americas, and in the Eastern Mediterranean and West African regions are under consideration and surveillance is expected to start in 2006.

✓ Generic protocol to measure the burden of pneumonia in developing countries

The collection of data to determine the burden of radiologically-confirmed pneumonia in Mozambique using a generic protocol was completed in 2005. Results of the study, which will also determine the appropriateness of the generic protocol, are expected during the first half of 2006.

* ✓= largely achieved ← = delayed or reprogrammed

✓ **Standardization and validation of serological assays to measure immune responses for pneumococcal conjugate vaccines**

The procedures for measurement of total serotype specific IgG by ELISA were standardized and two reference laboratories established to provide training reference materials and quality assurance for investigators wanting to standardize the assays in their laboratories. Criteria for evaluation of new vaccines/formulations based on antibody response using these methods were approved by the WHO Expert Committee on Biological Standardization and published in the WHO Technical Report Series.[1]

✓ **Two-year post vaccine introduction surveillance**

Preliminary results from the two-year post-vaccine introduction surveillance in South Africa and in Navajo population in the USA were presented at international conferences. Data showed that protection against invasive pneumococcal disease persists for up to four years after infant immunization. Follow-up in the native American population, in whom serotype coverage with the 7-valent vaccine is only around 50% and where the disease rates are the highest in the United States, showed that replacement disease is not a significant problem, four years after routine use of the vaccine. IVR provided financial support and monitored progress of the study, for which final reports are expected in early 2006.

✓ **Efficacy study of pneumococcal conjugate vaccine with radiological pneumonia as an endpoint**

The results of the efficacy study in the Gambia showed that the vaccine significantly reduced the incidence of pneumonia and overall childhood mortality.[2,3] The Philippines trial was also completed and the results expected during 2006. IVR provided technical support and monitoring of the conduct of both trials through an International Steering Committee and Data Safety Monitoring Board, in addition to providing financial support for the trial in the Gambia.

✓ **Safety and immunogenicity of a neonatal dose of pneumococcal conjugate vaccine**

The results of the initial safety phase of the study of a neonatal dose of pneumococcal conjugate vaccine were reviewed by the Data Safety Monitoring Board, and approval for continuation of the trial obtained. Enrolment of subjects for the safety and immunogenicity trial in Kenya is ongoing. IVR will monitor the conduct of the trial and continue to provide financial support.

2006–2007

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.

Milestones 2006–2007

- 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).

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Pneumococcal Vaccines Contacts

Dr Thomas Cherian, Coordinator

- www.who.int/vaccine_research/diseases/ari/en/index5.html
- www.who.int/topics/pneumococcal_infections/en/

SARS vaccines

FOCUS

Severe Acute Respiratory Syndrome (SARS) is "as the name implies" a severe respiratory illness caused by the SARS-associated coronavirus (SARS-CoV). The disease emerged in the People's Republic of China in 2002 and spread to countries within Asia, Europe and North America. The epidemic finally came to a halt in July 2003 through strict implementation of quarantine and isolation procedures, and international collaboration under the coordination of WHO. At the end of the outbreak, 8,437 cases had been identified and 9.6% of patients had died. Only sporadic cases have been reported since then, mainly linked to laboratory contamination. Although there is evidence that SARS-CoV emerged from a non-human source, no animal reservoir has yet been identified with certainty.

In 2004, half a dozen candidate vaccines were in development, including an inactivated vaccine which was tested in a Phase I clinical trial in China. All these vaccines face hurdles, not the least of which is the inability to establish their efficacy in humans in the absence of circulation of the disease.

Role of IVR

WHO was tasked by its Member States in 2003 to control the SARS epidemic by mobilizing global scientific research to improve understanding of the disease, and by developing tools such as diagnostic tests, drugs and vaccines that all countries could afford. IVR took up this challenge as facilitator of SARS vaccine research and development, to coordinate international information sharing and promote advances in SARS vaccines, especially in China.

Overview 2004–2005

Following recommendations by leading experts in the disease in 2003, IVR focused on three major issues: investigation of appropriate animal models to guide the development of SARS vaccines; development of regulatory and biosafety guidelines; and provision of support to regulatory authorities involved in SARS vaccine research. In addition to the activities and outcomes detailed below, a review was carried out with the identified SARS patent applicants on intellectual property rights. Although the concept to create a patent pool to facilitate development of SARS vaccines was not pursued due to waning interest in SARS vaccine production during 2005, it could be applied to other vaccines.

Finally, IVR supported a proposal from a Chinese scientist to develop a SARS sub-unit S-glycoprotein vaccine produced in the yeast *P. pastoris*. For technical reasons, the investigator did not succeed and the project was therefore terminated.

Reaching 2004–2005 milestones*

✓ International workshops on "Animal Models for the Development of SARS Vaccines"

Two technical meetings were convened to review progress on the development of SARS animal models. Valuable conclusions and recommendations were formulated on the usefulness of various models, and a consensus reached on the most appropriate ones. Participants also reviewed the results of experiments investigating whether inactivated SARS vaccines induce enhanced disease in animal models following infectious challenge with SARS-CoV, a phenomenon observed when studying vaccination of cats against a feline coronavirus. The meetings concluded that at present no data support the existence of this phenomenon.[1]

Finally, a decision was taken at the second meeting to set up a repository of coronavirus strains at the UK National Institute for Biological Standards and Control, and to develop reference reagents and sera for evaluation of candidate vaccines. This activity was ongoing in December 2005 in collaboration with colleagues at the WHO Department of Immunization, Vaccines and Biologicals.

* ✓= largely achieved ← = delayed or reprogrammed

✓ **Fact-finding mission in China to identify potential areas of collaboration and develop a jointly supported plan of activities**
The Ministry of Science and Technology of China and WHO held a joint workshop in Beijing in March 2004 on the development of vaccines against SARS and avian influenza. The workshop was attended by over 60 experts – scientists, physicians and ethicists – from China and around the world. Parallel meetings took place and visits to several institutions on various aspects of the vaccine programmes on SARS and influenza. The general consensus was that China had made much progress towards the development of a vaccine against SARS.

✓ **Safety/immunogenicity Phase I trials of inactivated SARS vaccines**
Following a request by the State Food and Drug Administration of China (SFDA), an expert meeting was convened in Geneva in May 2004 to provide guidance on the protocol produced by Sinovac, China, for the first Phase I clinical trial of an inactivated SARS vaccine in Beijing. As a result, the trial was conducted in agreement with international Good Clinical Practices. A similar meeting was organized in June 2005 to assist the SFDA with the analysis of the Phase 1 trial results and the design of a Phase II trial.

✓ **WHO recommendations and guidance documents in relation to regulatory aspects and biosafety in research and clinical trials**
Specific recommendations were not produced for SARS related vaccine research, but WHO guidelines for safe production of vaccines under biosafety level 3 conditions for other pathogens (e.g. wild type polioviruses used in the manufacture of inactivated poliovirus vaccines) were made available to manufacturers and regulators.

2006–2007

As there have been no SARS cases since mid 2004, IVR will continue to monitor the field of SARS vaccines but does not plan any specific activities in this area.

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SARS Vaccines Contacts

Dr Thomas Cherian, Coordinator

- www.who.int/vaccine_research/diseases/sars/en/
- www.who.int/topics/sars/en/

ETEC vaccines

FOCUS

The burden of disease of enterotoxigenic *Escherichia coli* (ETEC) diarrhoea is high, although more studies to update the figures and trends are called for. Longitudinal cohort studies of ETEC infection in infants in Bangladesh and Guinea Bissau highlight its endemic and widespread nature in this population in developing countries. Yet difficulties in culturing ETEC bacteria from fresh diarrhoeal stool specimens, and in identifying LT or ST toxin excreting strains or specific colonization factors have restricted studies to a few research laboratories.

Available and promising vaccines have been developed for travellers, but have not been designed for, nor undergone specific evaluation in infant populations living in regions of high disease burden where the vaccine is needed. The recent failure of one vaccine strain to offer protection to Egyptian infants is a major impediment to ETEC vaccine development, but underscores the need for the development of new vaccine strains and approaches for this target population.

Role of IVR

IVR has played a role in setting the agenda for ETEC vaccine research and development for children in developing countries where the disease is endemic. The international meeting hosted by IVR in 2003 identified the gaps in knowledge and developed a mid-term agenda for research into ETEC vaccines.

Overview 2004–2005

In addition to the activities listed below, IVR is establishing a Collaborating Centre for ETEC Research at Göteborg University in Sweden. The Centre will work towards the additional laboratory tools needed for the field, robust detection methods, and further laboratory analyses to define which colonization factors (CFs) or immunological markers of infection are important for vaccine development. IVR has also supported some preclinical evaluation of vaccine candidates, and facilitated further etiological and epidemiological studies that are being funded by other international groups.

Reaching 2004–2005 milestones*

← Surveillance activities for ETEC burden of disease in sub-Saharan Africa and Asia

It was anticipated to utilize the regional rotavirus networks to gather ETEC surveillance data in hospitalized infants and young children in some countries. However, only limited WHO-facilitated surveillance has been possible at individual research institutions due to a lack of funds, and the absence of a robust and easy-to-use laboratory assay for the detection of ETEC strains.

← A clinical trial to evaluate the killed ETEC vaccine in a developing country

The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) has been conducting a large-scale field study of the epidemiology and burden of disease of ETEC-associated diarrhoea, with a view to conducting a vaccine trial. Because of lack of funding, IVR has not been able to support this activity.

✓ Preclinical laboratory studies of ETEC vaccine candidates

Preclinical and laboratory studies of two ETEC vaccine candidates were supported by IVR, namely the live attenuated multivalent ETEC/Shigella vaccine candidate developed at the Center for Vaccine Development, USA and the killed whole cell vaccine with recombinant B-subunit of the cholera toxin in Göteborg University, Sweden. Manuscripts are in preparation for submission to scientific journals.

✓ Adult volunteer studies to evaluate proof-of-principle of the immunological and potential protective role of specific colonization factors

Pharmaceutical research companies are continuing their evaluation of various vaccine candidates and immunological assessment of correlates of protection. IVR

* ✓= largely achieved ← = delayed or reprogrammed

fulfilled its role to provide technical input to a study which will move soon to adult volunteers. IVR will further serve in an advisory role in the conduct of the clinical trial.

← Studies to identify distribution of important colonization factors in developing countries

More studies are required to supplement those being carried out in developing countries to examine the circulating CFs. IVR has provided technical advice and support through laboratory studies that may lead to a clearer idea of which CFs are circulating and may be protective of infection, and which diagnostic tools are optimal.

← Oral live attenuated vaccine Phase I/II clinical trials

This milestone has been reprogrammed since IVR's technical – and possible financial – contribution is dependent on progress and commitment outside its control.

2006–2007

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 CFs 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.

Milestones 2006–2007

- *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).

ETEC Vaccines Contacts

Dr M. Teresa Aguado, Coordinator

Dr Duncan Steele, Scientist

- www.who.int/vaccine_research/diseases/e_e_coli/en/
- www.who.int/topics/escherichia_coli_infections/en/

Rotavirus vaccines

FOCUS

The extent of the disease burden and mortality of rotavirus infection in infants and young children has led the international community to prioritize the development of a rotavirus vaccine. Yet the true disease burden is still unknown in some regions, and estimated death tolls vary depending on the source. Two vaccine candidates have completed large-scale Phase III clinical studies and have been registered, one in the USA and the other in Europe, in addition to a number of developing and middle-income countries. The bovine-human pentavalent reassortant vaccine has shown 95% protection against severe rotavirus disease requiring an emergency room visit or hospitalization in infants[1]. The human monovalent vaccine strain showed 85% protection against severe rotavirus gastroenteritis and against hospitalization in infants in Latin America[2]. However, the safety and efficacy of both candidates remains to be determined in African and Asian infants. Other candidate vaccines are being evaluated for potential development by vaccine producers in developing countries, particularly in the Asian region.

Role of IVR

In its leadership role in rotavirus vaccine development, IVR coordinates regional networks and financially supports the surveillance of rotavirus disease burden and cost-estimation studies. IVR also provides extensive technical guidance to rotavirus vaccine trials in developing countries in Africa and Asia. International consultations are convened and guidance and recommendations issued in collaboration with strategic partners such as the Rotavirus Accelerated Development and Introduction Plan of the Global Alliance on Vaccines and Immunization at PATH, and the Centers for Disease Control and Prevention (CDC), USA.

Overview 2004–2005

IVR expanded the regional networks for the surveillance of rotavirus disease burden to previously under-represented areas. The networks in Africa, North Africa and the Middle East and in Eastern Europe are coordinated and managed by WHO regional offices. With its strategic partners, IVR also facilitated networks in Asia and Latin America. Country-specific studies were conducted with IVR scientific and financial support on hospital-based disease burden, the costs of rotavirus infection and strain diversity. Clinical studies were conducted in developing countries, and meetings to discuss disease burden studies, regulatory reviews and laboratory training were held in all regions. In addition, IVR facilitated an international consultative meeting to consolidate the figures for rotavirus-associated mortality. These figures will be published in 2006 after consolidation of country data.

Support to research and development into upstream rotavirus vaccine candidates – i.e. those that have not yet entered large-scale clinical trials – has become a priority for IVR. Following the recommendation of the WHO Strategic Advisory Group of Experts (SAGE), IVR issued a call for proposals and provided support to one development project.

Reaching 2004–2005 milestones*

✓ **Economic estimates for rotavirus disease in developing countries**
Studies were completed in several countries on the costs associated with rotavirus infection in infants admitted to hospital and in the community. The studies utilized the WHO generic protocol developed for this purpose[3,4] and were sponsored by IVR in Bangladesh, Ghana and South Africa and by partners in Malawi, Uzbekistan and Viet Nam. An expert review and consultative meeting is scheduled to take place in March 2006 in Geneva.

✓ **Training curriculum for national regulatory authorities in potential early adopter developing countries to evaluate preclinical to clinical transition**
A training curriculum was developed by IVR and WHO's Quality, Safety and Standards team for the review of clinical dossiers on rotavirus vaccines. In

* ✓= largely achieved ← = delayed or reprogrammed

addition, rotavirus vaccines were discussed and reviewed by the Global Training Network and the Developing Country Vaccine Regulators Network. Regional meetings were held in Latin America (Argentina and Brazil), South-East Asia (Thailand) and Africa (Botswana, Ethiopia and South Africa) with the respective WHO regional offices.

✓ **Phase III efficacy trials in developing countries**

Clinical trials of the GSK Biologicals vaccine candidate were supported by the RAPID partnership and IVR in Africa and Asia. A preliminary immunogenicity study was completed in Bangladesh as well as a Phase II dose-ranging immunogenicity study in South African infants. Enrolment for a similar trial in Bangladeshi infants was completed and the results expected in the first half of 2006. A Phase II safety and immunogenicity study in HIV-infected infants was initiated in South Africa. The first large-scale Phase III efficacy study also started in South Africa, with expansion to Malawi planned for early 2006.

Regarding a second candidate vaccine, discussions with Merck Research Laboratories led to commitment by the company to provide human and financial resources to conduct Phase III studies in developing countries. The need for these studies was recognized by SAGE and will be funded by PATH. IVR will fulfil a technical advisory function.

✓ **Regulatory pathways for live rotavirus vaccine products**

The capacity strengthening of national regulatory authorities for the regulation of live oral rotavirus vaccines was achieved. International consultations were organized by IVR and the WHO Quality, Safety and Standards team to develop guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccines (oral). These guidelines were ratified by the Expert Committee on Biological Standardization in October 2005.[5]

2006–2007

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 alternative rotavirus vaccine candidates.

Milestones 2006–2007

- Consensus data on global mortality due to rotavirus are available (mid 2006).
- Clinical lots of an alternative 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).

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Rotavirus Vaccines Contacts

Dr M. Teresa Aguado, Coordinator

Dr Duncan Steele, Scientist

- www.who.int/vaccine_research/diseases/rotavirus/en/

Shigella vaccines

FOCUS

Estimations of global mortality rates in young children due to Shigella infection differ by a factor of 10 (670 000 versus 70 000 each year). It is therefore urgent that a consensus on the real burden of disease and Shigella-associated mortality is reached. Global studies have also reported increasing levels of antibiotic resistance, which hastens the need for a Shigella vaccine.

Research and development has progressed with several vaccine candidates in clinical evaluation and with IVR support for preclinical studies. It is generally agreed that a multivalent Shigella vaccine will be required, which increases the complexity of its development. Disparity in the results of vaccine trials in adult volunteers in industrialized countries compared to those in young children in developing countries has highlighted the need for the development of vaccine candidates targeted to infants in high-risk or endemic areas.

Role of IVR

IVR's contribution consists of highlighting research and development requirements through international consultations and supporting preclinical studies. WHO is also a strategic partner for the Diseases of the Most Impoverished (DOMI) initiative at the International Vaccine Institute (IVI), Republic of Korea.

Overview 2004–2005

IVR's role was reinforced at an international meeting that set the agenda for *Shigella* vaccine research and development for the next 5–10 years. Preclinical vaccine research was supported at the Center for Vaccine Development (USA), the University of Rome (Italy) and at the Institut Pasteur (France). IVR also co-organized the IVI/WHO DOMI meeting in Hanoi, Viet Nam in 2005 and chaired the discussions on *Shigella* vaccine R&D at this meeting. In addition, IVR has acted as an adviser to the Bill & Melinda Gates Foundation in preliminary meetings to develop a programme for enteric vaccine research. Finally, a review was organized of the field of *Shigella* vaccine research and burden of disease at the Global Vaccine Research Forum in Brazil in 2005.[1]

Reaching 2004–2005 milestones*

✓ The international technical meeting on "*Future needs for Shigella vaccine research for children in developing countries*" sets a mid- to long-term agenda

The meeting, held in September 2004, identified the following overall needs: burden of disease studies in various regions; epidemiological and genetic studies on circulating strains and antibiotic resistance patterns; and support to develop different vaccine approaches. A full report of the meeting will be published on the IVR web site[2], and a short report is available in the *Weekly Epidemiological Record*.[3]

← Surveillance activities for *Shigella* burden of disease in sub-Saharan Africa

Two proposals for surveillance activities in Africa were reviewed and approved by the Steering Committee, and are awaiting sufficient funding for implementation.

✓ Surveillance activities and translational studies in Asia

IVR is a partner of the DOMI project at IVI, and provided scientific advice and support to projects in several countries, including Bangladesh, the People's Republic of China and Pakistan. These studies highlighted the increasing antibiotic resistance in *Shigella* strains and an apparently increasing diversity of *Shigella* serotypes.[4,5,6]

* ✓= largely achieved ← = delayed or reprogrammed

← A live oral attenuated multivalent vaccine in a Phase I/II trial

The Centre for Vaccine Development, responsible for coordinating the trial, continues its programme of *Shigella* vaccine research. Although IVR supported some preclinical and animal studies of the live attenuated multivalent candidate, continued support, including for clinical trials, is dependent on further financial support.

← A Phase III trial of an oral live attenuated candidate vaccine (SC602) in a developing country

The Institut Pasteur is a major player in the area of *Shigella* vaccine research. IVR supported selected preclinical studies of the live attenuated *Shigella flexneri* candidate, and encouraged the continuation of vaccine trials in young children living in high-risk areas. IVR facilitated the interaction between a vaccine trial site in Kenya with ongoing *Shigella* surveillance in collaboration with the Institut Pasteur. Discussions are ongoing regarding a vaccine trial, and one site visit has been carried out.

← Studies to identify distribution of antibiotic resistance of circulating *Shigella* strains in some developing countries

Proposals of appropriate studies were reviewed and approved by the WHO Diarrhoeal Diseases Steering Committee. These studies will proceed as soon as the necessary funding is identified.

2006–2007

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.

Milestones 2006–2007

- *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).

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Shigella Vaccines Contacts

Dr M. Teresa Aguado, Coordinator

Dr Duncan Steele, Scientist

- www.who.int/vaccine_research/diseases/shigella/en/
- www.who.int/topics/shigella/en/

Dengue vaccines

FOCUS

Dengue is a mosquito-borne viral infection that is now endemic in over 100 countries across the globe. In addition, severity of disease is worsening, which may well be due to increased co-circulation of the four antigenically related dengue strains. Some 2500 million people are currently at risk from dengue, a leading cause of hospitalization of children in many endemic countries. Although effective supportive therapy exists for severe, haemorrhagic dengue, mortality can be considerable if the disease is not properly managed. Vector control is an important preventive strategy, yet vaccination remains the most promising long-term strategy to curb the disease.

Role of IVR

IVR provides guidance on evaluation and testing of dengue vaccines and contributes to shaping the agenda on underpinning research issues. This facilitating role is critical since considerable challenges face the clinical development of vaccine candidates because of complex disease epidemiology and concerns over vaccine-induced disease enhancement through immuno-pathological processes.

Overview 2004–2005

Work during this period focused on supportive research and reinforcing IVR's contribution as facilitator for the clinical testing of vaccines. Research was carried out on the validation of monkey models, the fine characterization of humoral immune responses to dengue virus and vaccine candidates, and on exploring novel strategies to attenuate dengue virus. The ultimate aim of this research is to increase the number of candidate dengue vaccines in the pipeline. To facilitate vaccine testing, international reference materials were established, and a consultation process initiated to define correlates for protection of dengue vaccines. IVR also collaborated with other WHO programmes and partners on improved diagnostics and a review of dengue case definitions.

Reaching 2004–2005 milestones*

✓ Standardized protocol for evaluation of vaccines in monkeys
IVR funded the development of the protocol, although the relatively low predictability of the monkey model for dengue disease has lowered interest in this model. The results and methods of the study will be available in early 2006.

✓ Studies on the mechanism of protection and immune enhancement
Fine characterization of immune responses in protection and pathology have been conducted using competitive ELISA and Biacore technologies. The human challenge model has been shown to be a viable strategy to measure vaccine-induced protective antibody responses.

✓ Cohort for Phase III trials of tetravalent vaccine in a developing country
IVR will provide guidance on field evaluation and criteria to assess long-term safety of dengue vaccines in the coming biennium. In relation to this target, a scientific consultation on correlates of protection for dengue vaccines was conducted in late 2005. WHO is collaborating with the Pediatric Dengue Vaccine Initiative (PDVI), which is establishing a network of field sites for epidemiological cohort studies and clinical evaluation of dengue vaccines.

In addition, exploratory research into novel strategies of dengue virus attenuation has been initiated, with the aim to broaden the pipeline of vaccine candidates.

* ✓= largely achieved ← = delayed or reprogrammed

2006–2007

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.

Milestones 2006–2007

- 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).

Dengue Vaccines Contacts

Dr Joachim Hombach, Scientist

- www.who.int/vaccine_research/diseases/vector/en/index.html
- www.who.int/topics/dengue/en/

Japanese encephalitis vaccines

FOCUS

Japanese encephalitis (JE) is the most common cause of viral encephalitis in the Asian Pacific region. The spread of the disease, transmitted by *Culex* mosquitoes, into non-endemic regions is intensified by the expansion of irrigated agricultural areas and the presence of amplifying hosts such as pigs. Some 50 000 cases of JE occur annually, with fatality rates reaching 25–30%, and up to 50% long-term disabilities in survivors. In the absence of an efficient therapy, prevention remains the most important strategy for disease control, especially through vaccination. While neural tissue-derived JE vaccines have helped to curb the disease in some countries, their widespread introduction has been hampered by cost, supply shortage and the need for multiple immunizations. Recent epidemics have led to increased demand and an accrued need for more effective and safe JE vaccines. In parallel, surveillance and diagnostic capabilities need to be improved to generate more accurate figures on the burden of disease.

Role of IVR

IVR facilitates the evaluation and registration of new JE vaccines through expert advice in relation to clinical trials and vaccine safety, technical specifications and other normative issues. In close collaboration with the WHO regional offices, IVR is also the focal point for accelerated JE vaccine introduction. A strategic partner in this activity is the Program for Appropriate Technology in Health (PATH).

Overview 2004–2005

IVR has been facilitating the clinical development and evaluation of new JE vaccines that hold promise for programmatic use in developing countries, including consultations on clinical trials, and normative activities on vaccine evaluation and registration. With the WHO Department of Immunization, Vaccines and Biologicals (IVB), IVR also focused on the harmonization and strengthening of surveillance through the development of standards and guidelines, and support to the diagnostic capabilities of public health laboratories.

Reaching 2004–2005 milestones*

✓ Evaluation of the yellow fever/JE chimeric vaccine
IVR held consultative meetings on the clinical development for paediatric indication of this candidate. To respond to the need for clinical development and evaluation of this and other JE vaccines and their introduction, IVR initiated the following activities during 2004–2005.

✓ Correlates of protection for JE vaccines
A scientific consultation was held to define the correlates of protection for JE vaccines. The correlates proposed by the experts were peer reviewed and subsequently endorsed by the WHO Expert Committee on Biological Standardization.[1]

✓ Harmonization and strengthening of surveillance
The surveillance standards developed during an IVB/IVR consensus-building workshop were finalized and will be field tested during 2006.[2]

✓ Preparation for the introduction of new JE vaccines
With IVB, WHO regional offices and PATH, a country consultation process on how to prepare for the introduction of new vaccines and the expansion of paediatric vaccination was launched at a meeting of the WHO South-East Asia and Western Pacific regions.[3]

✓ Production and safety of the live attenuated JE vaccine
The safety of the live attenuated vaccine SA 14-14-2 was reviewed by the WHO Global Advisory Committee on Vaccine Safety, building on the guidelines for

* ✓= largely achieved ← = delayed or reprogrammed

production and quality control of live attenuated JE vaccines[4]. The recommendations were published in the *Weekly Epidemiological Record*.[5]

2006–2007

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.

Milestones 2006–2007

- 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).

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Japanese Encephalitis Vaccines Contacts

Dr Joachim Hombach, Scientist

- www.who.int/vaccine_research/diseases/japanese_encephalitis/en/
- www.who.int/topics/encephalitis_viruses_japanese/en/

Human papillomavirus vaccines

FOCUS

Eighty per cent of cervical cancer mortality – causing about 250 000 deaths each year – occurs in women in developing countries. Virtually all cervical cancer cases are linked to genital infection with human papillomavirus (HPV), and about 70% of cases are due to types 16 and 18, with some regional variation. Vaccination against HPV infection is a potentially cost-effective way to reduce the incidence of cervical cancer, and may be especially valuable in settings where effective screening and early treatment programmes have been difficult to implement.

Two candidate HPV vaccines against types 16 and 18 (one of which is also effective against types 6 and 11 that cause genital warts) are in advanced stages of clinical evaluation. Both showed high efficacy in proof-of-principle studies, and one manufacturer reported almost 100% protection against high-grade cervical cancer precursor lesions caused by HPV types 16 and 18 in women aged 16–25 years. Bridging studies for relevant age groups (9–15 and over 25 years) have been completed, which will expand the delivery options.

Role of IVR

WHO has been working for many years to facilitate HPV vaccine evaluation and to prepare for global introduction. These goals have been pursued through consultative discussions with the international scientific and public health community, consensus building among opinion leaders, and coordination of efforts among stakeholders in the public and private sector, in both developing and industrialized countries.

Overview 2004–2005

IVR's contribution to the two vaccine candidates described above has been the following:

- Facilitating the evaluation and review of clinical data through consultations to develop consensus on endpoints for vaccine trials;
- Harmonizing and standardizing laboratory procedures through development of standard reagents and preparing for a global HPV Laboratory Network to facilitate vaccine evaluation and monitoring in developing countries;[1]
- Creating a multi-disciplinary policy platform to set a global agenda for future HPV vaccine introduction, in consultation with partner agencies, regions and countries;
- Preparing the establishment of a WHO Information Centre on HPV and Cervical Cancer.

Through well-targeted efforts, IVR has been able to move the HPV agenda forward with major players in the field, with relatively modest financial investment. A continued dialogue has been maintained with both the public sector and vaccine producers, and a comprehensive plan developed by IVR for accelerated introduction, which led to significant new funding for the HPV vaccine field. These resources have benefited the WHO Department of Immunization, Vaccines and Biologicals for selected activities, and more specifically IVR for laboratory network development, a specialized information centre and vaccine introduction guidelines.[2]

Reaching 2004–2005 milestones*

✓ Analysis of the acceptability and feasibility of HPV vaccination in developing countries in preparation for preclinical testing and eventual introduction of novel HPV vaccines

Consultations were held in four countries over the biennium to raise awareness of the burden of cervical cancer, and to discuss key issues that need to be addressed in determining the role of HPV vaccines in comprehensive cervical cancer control programmes. These issues were discussed further during the HPV Expert Advisory Group[3,4] and other meetings with partner agencies. Questions

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include the objectives of an HPV vaccination programme (direct protection of women against cervical cancer, or prevention of transmission of HPV infection); the target age group for vaccination; the characteristics of the vaccine (e.g. efficacy and effectiveness; number of doses needed; safety and efficacy in immuno-compromised persons and in pregnant women); the delivery strategies available to reach the target populations; and the cost–effectiveness and affordability of the vaccine.

✓ **Cost–effectiveness modelling of HPV vaccination in Asia and Africa**
Two exploratory modelling studies on cost–effectiveness analysis of cervical cancer prevention strategies were carried out with financial support from IVR. The modelling analysis applied to the United Republic of Tanzania, where the reported cervical cancer incidence is the highest in Africa, suggests that HPV vaccination could be cost effective, either alone or in combination with a one-time screening. In India, a comparison of strategies to reduce cancer suggests that the age of the person vaccinated and the duration of vaccine efficacy will influence the relative effectiveness of vaccination.

← **Country-specific on-line database on HPV and cervical cancer burden**
A WHO HPV information centre will be established in 2006 (see 2006–2007 milestones) and managed by the Institut Català d'Oncologia (Catalan Institute of Oncology) in Barcelona, Spain with funding from IVR.

✓ **Studies on HPV type prevalence in selected Asian and African developing countries with high disease burden**
Priority issues on HPV epidemiology were identified during the biennium and expanded at the HPV Expert Advisory Group meeting[1], which made the following recommendations. Further data are needed on HPV genotype distribution among women with cervical cancer and in women with normal cytology, in areas of the world where there is currently very little information such as Africa, the People's Republic of China, Central Asia and the Middle East. Reasons for differences in age-specific prevalence, such as variation in age at onset of sexual activity in different areas and variation in prevalence of causes of immune impairment (parasites, HIV, etc.), should be investigated. Data on other HPV-related cancers, including penile, anal, vulvar, vaginal and oro-pharyngeal cancers, would also be valuable.

2006–2007

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.

Milestones 2006–2007

- 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).

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Human Papillomavirus Vaccines Contacts

Dr M. Teresa Aguado, Coordinator

Dr Felicity Cutts, Medical Officer

Dr Sonia Pagliusi, Scientist

- www.who.int/vaccine_research/diseases/viral_cancers/en/index3.html

Meningococcal vaccines

FOCUS

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, and where serogroup A meningococcus is the predominant cause of epidemic meningitis. Despite treatment, at least 10% of patients die within days of onset and 10–20% of survivors develop significant neurological sequelae. The recent development of meningococcal conjugate vaccines offers a good prospect for more effective prevention strategies to control the disease.

The Meningitis Vaccine Project (MVP), created in 2001, is a 10-year partnership between WHO and the Program for Appropriate Technology in Health (PATH)[1]. The project's goal is to eliminate epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, introduction, and widespread use of conjugate meningococcal vaccines. MVP has used an innovative method to develop a Men A conjugate vaccine at a target price of US$ 0.40 per dose.

Role of IVR

IVR and the WHO Regional Office for Africa significantly contribute to the development of a Men A conjugate vaccine, particularly in the following areas: 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 to plan for the advent of conjugate vaccines. WHO will become increasingly involved with the introduction plans for the vaccine in Africa.

Overview 2004–2005

During 2004–05, WHO worked to reinforce partnerships with countries to enhance surveillance and to ensure the development of a safe vaccine according to international standards. In parallel, MVP focused on capacity building at all levels, from strengthening national regula-tory authorities and ethical review proficiency, to supporting countries to implement and sustain high standards of surveillance. The clinical development of the Men A conjugate vaccine started with the Phase I trial in India among adult volunteers. Sites for the Phase II studies were selected in Africa and preliminary activities conducted. A draft strategic plan for Men A conjugate vac-cine introduction was developed by the WHO Regional Office for Africa with input from all partners. Finally, a consultation on meningococcal carriage studies in Africa reviewed current knowledge and elaborated a research agenda to prepare for introduction of the Men A conjugate vaccine.[2]

Reaching 2004–2005 milestones*

✓ **Regional and national epidemic meningococcal disease surveillance systems to evaluate the importance of serogroup W135 as a potential epidemic strain in African meningitis belt countries**
Fourteen countries in the African meningitis belt have developed and implemented standard operating procedures for enhancing meningitis surveillance and laboratory capacity. A multidisciplinary team (epidemiologist, microbiologist, data manager) based in the WHO Multi Disease Surveillance Centre in Burkina Faso provides direct support to countries and produces a weekly epidemiological Bulletin shared among countries and partners.

✓ **Standardization and validation of serological assays to measure immune responses for serogroup A meningococcal conjugate vaccine**
Standard operating procedures have been harmonized among laboratories performing the serological assays to measure the immune and functional antibody responses induced by the Men A conjugate vaccine. A working group has been

* ✓= largely achieved ← = delayed or reprogrammed

established to pursue this process, which will be fine-tuned with the testing of the Phase I sera.

← **Specifications, quality control procedures and a forecasting demand model for serogroup A conjugate vaccine**
These activities have been rescheduled for 2006–2007 as part of the overall regional vaccine introduction plan.

✓ **Production and quality control of a GMP batch of a conjugate meningococcal vaccine**
Three clinical batches of Men A conjugate vaccine were prepared for the Phase I clinical trial in India. After internal testing and control, these batches successfully underwent full preclinical testing (toxicology, physico-chemical and immunogenicity). Investigations on the conjugation process to optimize the yields and to finalize analytical methods, including consistency and stability studies, are being pursued. This work is overseen by the MVP team.

✓ **Comprehensive overview of past and current meningococcal meningitis situation in African target countries, including assessment of serogroup W135 as a potential epidemic strain**
The past and present situation of meningococcal meningitis was comprehensively assessed for three core countries in the African meningitis belt (Burkina Faso, Mali, Niger), integrating docu-mentation on disease burden, strain circulation, and meningococcal polysaccharide vaccine use. Country reports and a full analysis are being finalized, and the overall historical setting in Africa is being summarized. Retrospective mapping of intervention areas in the meningitis belt was developed using standardized indicators. This work is being expanded in close partnership with countries and WHO collaborating centres to develop a full information system and meningitis web site within the WHO Global Atlas[3]. This will be a useful tool for advocacy and research activities.

✓ **Regional-based plan for meningococcal conjugate vaccine introduction (WHO Regional Offices for Africa and the Eastern Mediterranean)**
The WHO Regional Office for Africa took the lead in developing a comprehensive strategic plan for Men A conjugate vaccine introduction with significant input from countries and partners. This will be submitted to the next Project Advisory Group in March 2006.

✓ **Financing plan for Men A conjugate vaccine in target countries**
A funding mechanism has been included in the above-mentioned strategic plan for vaccine introduction, and shared with countries in the meningitis belt.

✓ **Phase I safety and immunogenicity study (healthy adult volunteers) of serogroup A meningococcal conjugate vaccine**
The Phase I clinical study was conducted in Mumbai and Hyderabad in India and no serious adverse events reported. The serology testing (4-week immunogenicity samples) and the final 4-week study report are expected in early 2006.

✓ **Validation of a regulatory strategy for the selected product**
Following two training courses for 16 national regulatory authorities, a workshop on regulatory procedures for clinical evaluation of vaccines allowed target countries to cultivate a regional approach. This will be used in the next stage as a joint review of the Phase II clinical trial in Africa.

2006–2007

In the next biennium, the MVP team will continue its dedicated support to the development of a Men A conjugate vaccine as described above. 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.

Milestones 2006–2007

- 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).

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Meningogoccal Vaccines Contacts

Dr M. Teresa Aguado, Coordinator

Dr Marie-Pierre Preziozi, Scientist

Professor Kader Konde, Scientist, WHO Regional Office for Africa

- www.who.int/topics/meningitis/en/
- www.who.int/vaccine_research/diseases/meningitis/en/
- www.meningvax.org/

Capacity building in Good Clinical Practice and bioethics

FOCUS

Before a new vaccine is introduced in a developing country, it should be tested in representative populations using relevant schedules and endpoints. Furthermore, some vaccines are only likely to be required "and hence evaluated for efficacy" in developing countries. All vaccine trials should meet Good Clinical Practice (GCP), and ethical and applicable regulatory requirements. However, most institutes and clinical sites located in developing countries with a high prevalence of diseases such as malaria, tuberculosis or AIDS, have no experience in GCP, nor the capacity to conduct good quality trials or ethical reviews. Capacity building for research institutes in developing countries to conduct such trials is therefore a priority.

Role of IVR

As the vaccine research wing of WHO, IVR strengthens the capacity of selected clinical trial sites in developing countries to conduct vaccine studies with adherence to GCP guidelines and bioethical review standards. The strategic partner for these activities is the UNICEF/UNDP/ World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).

Overview 2004–2005

As trial sponsor, IVR implemented the site assessment, and prepared and initiated the Phase II open label safety, immunogenicity and reactogenicity trial of Mencevax ACW135 polysaccharide vaccine in Ethiopia. Preparatory activities were also carried out for the measles aerosol vaccine clinical trials in India and Mexico. In addition, activities related to capacity building for GCP implementation were conducted for projects on pneumococcal, malaria and Japanese encephalitis candidate vaccines in a number of countries.

For the core GCP training, a curriculum for workshops focusing on vaccine clinical investigators was developed, and two workshops for HIV and malaria vaccine investigators conducted in the United Republic of Tanzania and Thailand respectively, attended by more than 60 investigators from countries with high burden of the two diseases.

In response to requests from researchers, IVR is developing generic guidelines in the form of a core data set and standard definitions for the conduct of neonatal vaccine trials. These guidelines, produced with the Brighton Collaboration, will be available in mid 2006.

Reaching 2004–2005 milestones*

✓ Trial site database indicating areas where GCP or bioethics training is needed

A questionnaire was field tested at vaccine trial sites for measles aerosol and tuberculosis vaccines. Using the data obtained, GCP training was conducted for the measles aerosol vaccine trials at sites in India and Mexico. A web version of the questionnaire for the IVR vaccine trial site database was pilot tested, and a formal survey to collect site information initiated.[1] The database will be built up progressively from this baseline information. Potential trial sites can be grouped by geographical location and needs for capacity strengthening. The database will be updated and evaluated at regular intervals.

✓ GCP country-level training at an IVR-sponsored clinical trial site

On-site training in GCP core knowledge and implementation focused on the measles aerosol vaccine Phase I and II trials in India and Mexico, and the

* ✓= largely achieved ← = delayed or reprogrammed

meningitis polysaccharide vaccine Phase II trial in Ethiopia. Investigators from within the relevant country were trained, inter alia, in GCP, protocol development and implementation, informed consent procedures for volunteer participants, establishing a Data Safety Monitoring Board and Standard Operating Procedures.

✓ **GCP training for a specific regional-level clinical trial**

Two ICH-GCP (International Conference on Harmonization Guideline for Good Clinical Practice) training workshops were conducted for HIV and malaria vaccine investigators. The first one took place in Zanzibar, United Republic of Tanzania in April 2005, with participants from 13 countries in south-east Africa. This workshop was organized in collaboration with TDR, the African Malaria Network Trust and the African AIDS Vaccine Programme. The second workshop, held in Bangkok, Thailand in November 2005 for participants from 10 countries in Asia, was carried out in collaboration with TDR and the Mahidol University.

Participants were the main researchers in countries with a high burden of HIV and malaria, and are likely to be principal investigators for vaccine trials in the future. The IVR GCP training course and material for vaccine clinical investigators, including GCP basic knowledge, vaccine product development, trial implementation, ethics in vaccine trials and regulatory requirements, will be used in future training.[2]

✓ **Sponsorship of investigators to attend a regional workshop on bioethics or combined GCP-bioethics training concomitant with workshops sponsored by IVR partners**

In order to help strengthen national and/or institutional ethical review boards, IVR invited speakers to facilitate and provide training in ethical issues at two ICH-GCP training workshops. This activity was made possible through collaboration between WHO/SIDCER (Strategic Initiative for Developing Capacity in Ethical Review) and FERCAP (Forum for Ethical Review Committees in Asia and the Western Pacific Region).

2006–2007

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.

Milestones 2006–2007

- 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).

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1 Global Health Atlas, www.who.int/globalatlas.

2 Training workshop on ICH-GCP for clinical investigators focusing on HIV/AIDS and malaria vaccine trials, Bangkok, 21–25 November 2005. Programme description and list of materials (available from IVR Secretariat).

3 TDR Workbook for investigators. 2002. TDR/PRD/GCP/02.1b.

Capacity building in Good Clinical Practice and Bioethics Contacts

Dr Thomas Cherian, Coordinator

Dr Enbo Ma, Clinical Trials Specialist

- www.who.int/vaccine_research/about/en/
- www.who.int/topics/clinical_trials/en/
- www.who.int/topics/ethics/en/

Measles aerosol vaccines

FOCUS

Measles remains a major cause of morbidity and mortality in developing countries. Alternative routes of administration, using existing measles vaccine, may enhance control of the disease and reduce logistic and safety concerns.

The goal of the Measles Aerosol Project is the licensing of at least one method for respiratory delivery of measles vaccine. Three devices for aerosol administration of reconstituted vaccine and, if feasible, a dry powder device will enter the studies. The assumptions are that the aerosol devices will use currently licensed vaccines, and target children between 12 and 59 months for routine vaccination, and nine months to 18 years for mass campaigns. The objective is to complete clinical testing by 2009.

Role of IVR

IVR coordinates the Measles Aerosol Project in collaboration with the US Centers for Disease Control and Prevention and the American Red Cross.

Overview 2004–2005

Over the past 24 months the project established managerial and advisory groups; defined an efficient regulatory pathway, and performance and usability criteria for device selection; and selected devices for clinical trials. Animal and toxicology studies were completed, protocols developed and sites selected for Phase I clinical trials in India and Phase II in Mexico. Finally, requirements were outlined for a business and introduction plan, and for an economic assessment.

Reaching 2004–2005 milestones*

✓ Preclinical studies to characterize the performance of selected nebulizers and criteria for device selection

An expert panel reviewed the results of a bench study to define the performance characteristics of the Classic Mexican Device, and the standard operating procedures for characterization of candidate devices. A method for the rapid assessment of vaccine degradation during nebulization was developed by a Global Measles Specialized Laboratory. Field design requirements for vaccine aerosol delivery devices were drawn up. Three devices were selected from companies with products licensed in several countries and capacity to produce the devices under Good Manufacturing Practice, in sufficient quantities and at prices that the public health sector of developing countries can afford.

✓ Economic analyses

The primary objective of the studies is to develop and validate standard criteria on the need to introduce new vaccines (delivery and/or formulations) using measles as a case-study. Specifi-cally, the studies will: (i) identify criteria to evaluate new vaccines; (ii) estimate the level of effectiveness needed for a new vaccine/delivery method; and (iii) estimate what costs are reasonable for an alternative to the current vaccine. An incremental cost–effectiveness evalua-tion of aerosolised measles vaccines compared to the injectable vaccine will be carried out. In 2005, a study design was agreed upon and developed that will be implemented during 2006–2007.

✓ Investigational New Drug dossier (IND) for Phase I in India

The results of bench testing of delivery devices and methods, animal studies of safety and immunology, and Good Laboratory Practice toxicology studies supported the application in October 2005 of an IND dossier for a Phase I trial

* ✓= largely achieved ← = delayed or reprogrammed

in adults, followed by a trial in children. This activity is carried out in collaboration with the Serum Institute of India.

✓ **Phase I clinical study to determine the safety of aerosol administration of live Edmonston Zagreb attenuated measles vaccine in healthy volunteers in India**
The design for the clinical study is open, non-controlled and sequential by age. The overall safety of the vaccine will be evaluated for a year after vaccination in the 60 trial subjects per site. The trial has obtained approval to start by the Indian regulatory authorities, and GCP training for the full clinical study team of the three selected sites will be given before trials begin in early 2006.

✓ **Phase II clinical trials: suitable methods, potential trial sites, clinical protocol and application to the National Regulatory Authority**
The National Institute of Health of Mexico, international experts and WHO peer reviewed a Phase II protocol to meet Mexican and international standards. The protocol compares the safety and immunogenicity of a first dose to 12-month-old children in a five-arm study design: (i) subcutaneous (control); (ii) Mexican traditional device (reference); (iii) unvented jet nebulizer (Omron); (iv) breath-enhanced jet nebulizer (Trudell); and (v) micropump nebulizer (Aerogen).

The Phase II protocol was approved by the Ethics, Biosafety, and Research Commissions at the INSP, and by the WHO Ethics Review Committee. The IND dossier for the Phase II trial was submitted to the Mexican regulatory authority in December 2005. This activity is carried out in collaboration with the Serum Institute of India.

2006–2007

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. The activities described above 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, wheeze and respiratory distress, will be monitored. The planned duration of follow-up is 12 months.

Milestones 2006–2007

- 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).

Measles Aerosol Vaccines Contacts

Dr M. Teresa Aguado, Coordinator

Dr Ana Maria Henao Restrepo, Scientist

- www.who.int/vaccine_research/diseases/measles/en/

New vaccine delivery systems

FOCUS

Currently, most vaccines are given by needle and syringe injection. Without effective quality management systems and skilled personnel, this can result in disease transmission through unsafe injection practices and large volumes of hazardous waste. Needle-free delivery systems would also greatly facilitate vaccine administration. Most vaccines depend on the cold chain, which is not always functional and adds to the cost of immunization. Rendering vaccines thermostable would overcome this barrier. The number of administrations needed to achieve effective immunity, particularly in developing countries, could be reduced through the use of novel adjuvants or antigen delivery systems. These are but a few of the technical and logistical challenges that need to be addressed to improve the efficacy of vaccination programmes worldwide.

Role of IVR

IVR identifies promising novel vaccine delivery systems and provides seed money for research that could lead to their development, production and use in developing countries. To achieve this, IVR works with a Steering Committee of independent experts to prioritize technologies that will have the greatest impact in specific regional settings.

Overview 2004–2005

A number of needle-free delivery systems were evaluated for their safety, efficacy, and likely uptake and accessibility. Multi-dose jet injectors were considered too difficult to pursue for safety reasons. High-speed disposable cartridge jet injectors, although safe, were deemed to be too heavy when evaluated in acceptability trials in Africa. IVR therefore supported the development of optimal designs for small, hand-held, mono-dose jet injectors for use in developing countries. In addition, a preclinical evaluation of biodegradable implants that could permit needle-free delivery of dry vaccine, as well as clinical evaluation of a vaccine in the form of a patch, were undertaken. Finally, to promote the development and use of formulations that could improve vaccine efficacy, IVR held consultations on oral delivery of vaccines, vaccine stabilization methods and adjuvants.

Reaching 2004–2005 milestones*

✓ Review of the safety status of multi-dose jet injectors
A meeting of experts reviewed available data on the maximum quantity of residual blood that could be accepted as safe if transmitted from one vaccine to the next during use of a multi-dose jet injector. It was agreed that no surrogate markers of safety were acceptable for registration, and that multi-dose jet injectors could therefore not be considered absolutely safe. It was recommended that IVR should concentrate on devices for which there is zero risk of blood contamination.

✓ Development of a projectile/implant (ballistic) subcutaneous delivery system
Preclinical evaluation of the immunogenicity and stability of measles and hepatitis B vaccines in biodegradable implants was conducted in collaboration with Injectile, a company developing projectile-based vaccine delivery systems. Since the results were promising, IVR will support the further preclinical development required before a Phase I/II clinical trial can proceed.

✓ Additional needle-free proof-of-principle studies (transdermal or nasal)
A Phase 1 clinical trial of the transcutaneous application of measles vaccine was conducted. Preliminary results showed that transcutaneous immunization appears more efficient than sub-cutaneous immunization at raising mucosal immunity

* ✓= largely achieved ← = delayed or reprogrammed

against measles, although it fails to produce a detectable boost of circulating antibodies.[1] This approach, as that for nasal delivery, will not be pursued in 2006–2007 since other strategies were deemed more promising.

✓ **Feasibility of using cryoprotectants to overcome vaccine freezing**
Data suggesting that damage from freezing is a major contributor of vaccine wastage were reviewed by the Steering Committee on New Vaccine Delivery Systems, along with a proposal that adding cryoprotectants to existing vaccines would overcome the problem. The Committee considered that, while scientifically feasible, the regulatory pathway to licensure of such reformulated products was too complex to warrant pursuing by IVR.

2006–2007

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 research and development 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.

Milestones 2006–2007

- 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 competed (mid 2007).
- International consensus on the regulatory pathway for introduction of jet injectors for vaccine delivery is reached (late 2006).

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[1] Manuscript Phase I/II clinical trial of transcutaneous vaccination with the live attenuated measles vaccine ROUVAX® (in preparation).

New Vaccine Delivery Systems Contacts

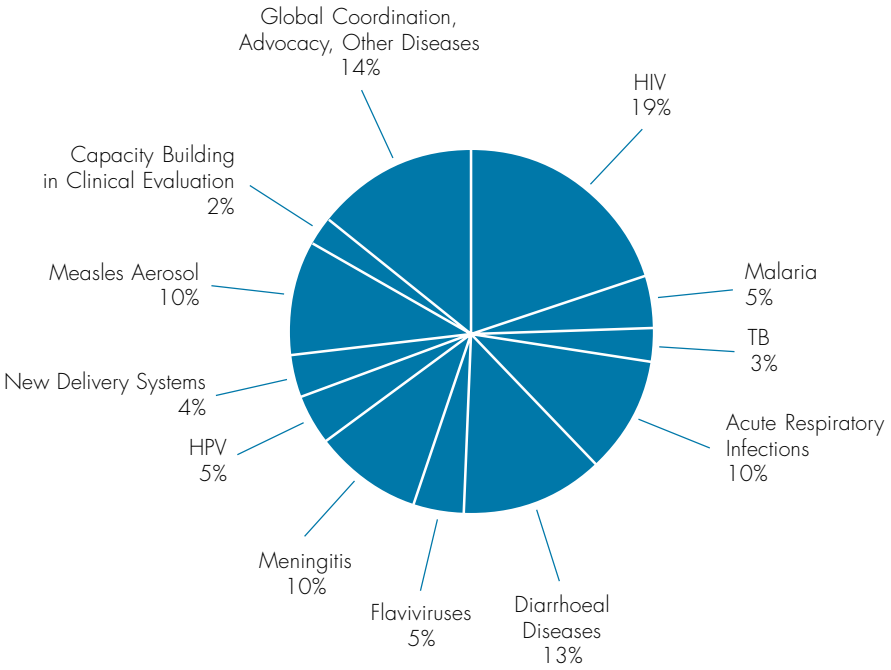
Dr M. Teresa Aguado, Coordinator

Dr Martin Friede, Scientist

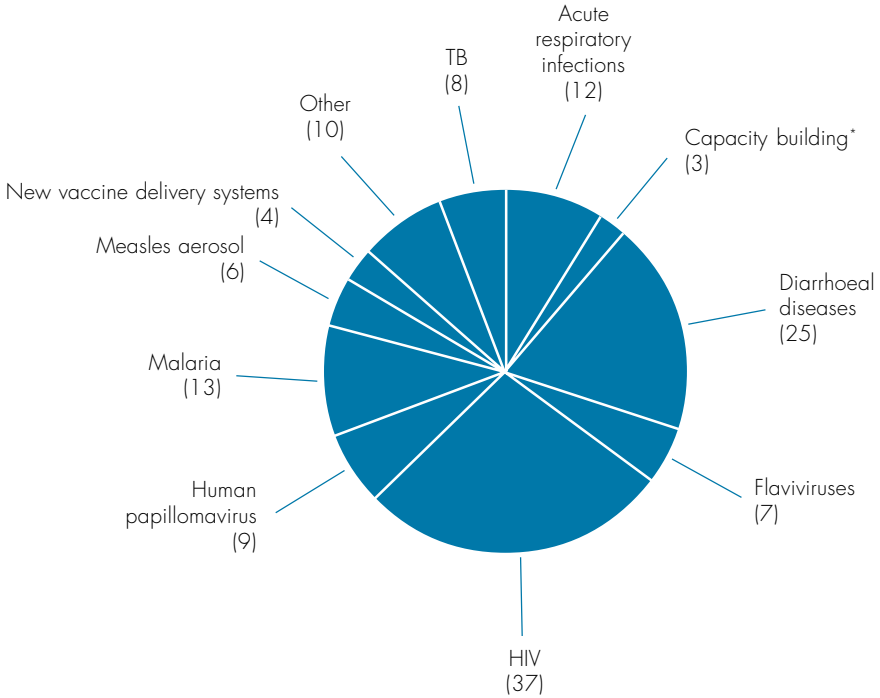
- www.who.int/vaccine_research/about/en/

Annex 1. IVR Resources

Total expenditure in 2004–2005 was US$19 615 000, an increase of more than 40% over the previous biennium. Distribution by disease and technology area was as follows.



Annex 2: IVR database of vaccine research projects



Number of vaccine research projects supported by IVR during 2004-2005 by disease/theme (total 134)

NB. In addition to these projects, capacity building, including ethical review, is an inherent component of many of the disease-focused projects.

Annex 3. IVR publications

In addition to the following articles that were published during 2004–2005 with input from IVR scientists, a number of research articles have been prepared for publication by principal investigators of IVR-sponsored vaccine research. These will be compiled during 2006 and their references published on the IVR Internet site.

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Annex 4: IVR steering committees and advisory groups

- Steering Committee on dengue and other flaviviruses vaccines
- Steering Committee on research related to measles vaccines and vaccination
- Steering Committee on new tuberculosis vaccines
- Steering Committee on new vaccine delivery systems
- Steering Committee on diarrhoeal disease vaccines
- Steering Committee of the African AIDS Vaccine Programme (AAVP)
- Advisory Committee for malaria vaccines (MALVAC)
- HIV Vaccine Advisory Committee (VAC)
- Product Development Group for the Measles Aerosol Project (PDG)
- Project Advisory Group for the Meningitis Vaccine Project (PAG)

The IVR Advisory Committee was established to give overall technical and strategic guidance. The Committee comprises 10-12 experts who represent a broad range of biomedical sciences, product development and other disciplines required for IVR activities. This Committee meets once a year.

IVR's workplan also takes into consideration the recommendations received from two other targeted advisory groups: the TDR Scientific and Technical Advisory Committee and the Immunization, Vaccines and Biologicals Strategic Advisory Group of Experts.

IVR's vision

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

www.who.int/vaccine_research

Vaccines are the cornerstone of contemporary medicine and are considered the best approach to reduce morbidity and mortality due to infectious disease.
Injecting hope, *Nature Medicine* 11, S1 (2005)

World Health Organization

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Initiative for Vaccine Research
Department of Immunization, Vaccines and Biologicals
World Health Organization
1211 Geneva 27 Switzerland
e-mail: VaccineResearch@who.int