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WORLD HEALTH ORGANIZATION

The Initiative for Vaccine Research

Report 2002-2003

WHO Department of Immunization, Vaccines and Biologicals

www.who.int/vaccine_research

IVR s mission

to guide, provide vision, advocacy, coordination, guidance and support to enable the development of safe, effective, affordable and accessible vaccines against infectious diseases of public health importance, especially in developing countries.

WORLD HEALTH ORGANIZATION

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WORLD HEALTH ORGANIZATION

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MALARIA VACCINES

WHO and the UNDP/World Bank/WHO *Special Programme for Research and Training in Tropical Diseases* (TDR) worked together during 2002-2003 to support malaria vaccine research and development. One of the main achievements is the initiation of a Phase I clinical trial of a promising blood stage vaccine candidate *Plasmodium falciparum* chimeric protein (PfCP-2.9) in Shanghai, China in August 2003. In addition, WHO has been appointed as the focal point for an informal grouping of major malaria vaccine funding agencies. This sharing of information and updates on malaria vaccine development efforts by each agency will hopefully promote targeted research activities - closing some of the knowledge gaps in malaria vaccine development.

HIV/AIDS VACCINES

A major target in this area has been the development of the African AIDS Vaccine Programme (AAVP), a network for African scientists and communities to promote and facilitate HIV vaccine research and evaluation through capacity building and promotion of regional and international collaboration. The AAVP advocates and supports a coordinated effort to contribute to global HIV vaccine development, ensuring that appropriate vaccines are developed and made accessible in Africa. AAVP activities are guided by specific milestones with an overall goal of facilitating the conduct of all stages of clinical trials in Africa over a ten-year period.

Moreover, WHO continued providing technical and targeted financial support to countries for the development of their National AIDS Vaccine Plans or Strategies (14 countries in total). These define overall national policies and frameworks, as well as plans to develop national infrastructures and capacity, ensuring the appropriate scientific and ethical standards of HIV vaccine-related research and clinical trials.

TUBERCULOSIS VACCINES

A network of laboratories for testing tuberculosis vaccine candidates in non-human primates was established. This consists of three laboratories already involved in TB research (Netherlands, Philippines, USA), and two additional ones (China, United Kingdom) that are intending to build capacity to perform challenge studies in primates (*M. fascicularis*).

Potential clinical Phase III testing sites for vaccines in Asian high burden countries identified (Bangladesh, Philippines). Capacity strengthening activities initiated in the Philippines.

MEASLES VACCINES

The Measles Aerosol Project was established in partnership with the Centers for Disease Control and Prevention (CDC), USA, and the American Red Cross, with financial support from the Bill and Melinda Gates Foundation. Its goal is to license at least one method for respiratory delivery of currently available measles vaccines, which will provide a means that is potentially cheaper, safer and easier than injection. Target for completion of clinical testings: 2007-2009.

PARTNERSHIP WITH THE GLOBAL ALLIANCE FOR VACCINE AND IMMUNIZATION (GAVI)

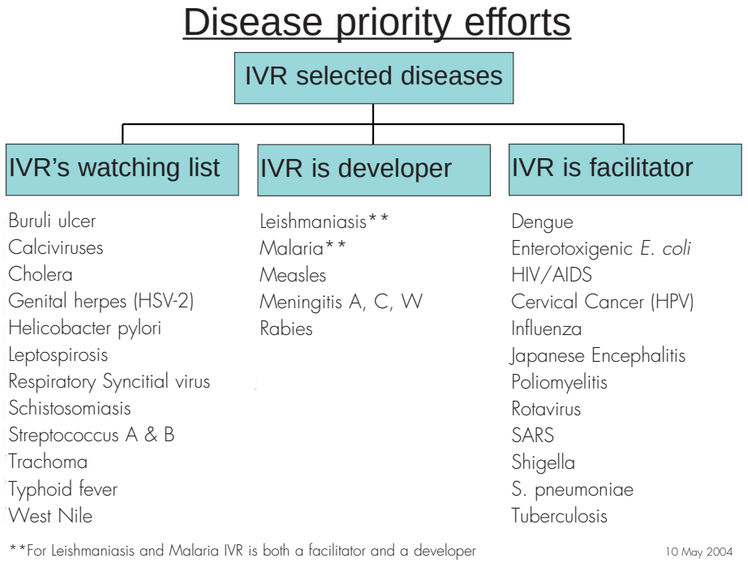
GAVI prioritized the need for pneumococcus and rotavirus vaccine development and has implemented specific programmes to accelerate their development and introduction. These programmes, the Accelerated Development and Introduction Plans (ADIPs), were created at the Johns Hopkins University in Baltimore and at the Programme for Appropriate Technology in Health (PATH) in Seattle, respectively. During 2002-2003, WHO played a catalytic role in conceptualising and developing the ADIP plans and hosted the secretariats of the Interim ADIPs, until the permanent teams were established. IVR remains a strategic partner of both ADIPs and is involved centrally in the research activities of these programmes.

IVR - A Priority-Setting Framework

The starting point for the IVR prioritization process is the recognition of "all infectious diseases of public health importance". Several criteria are then applied. For example, WHO's commitment to reach measles mortality-reduction objectives means that measles vaccine R&D is a high priority even though an effective inexpensive vaccine against measles already exists. However, a vaccine against African trypanosomiasis is not included, on the grounds of a comprehensive analysis conducted by the UNDP/World Bank/WHO *Special Programme for Research and Training in Tropical Diseases* (TDR) and endorsed by TDR's governing bodies.

Three filters are used to select target infectious diseases. This allows IVR to focus its vaccine R&D portfolio on diseases: a) which do not have effective affordable vaccines, b) where no alternative treatment tools exist which could be implemented without major logistical hurdles, c) which do not represent an attractive commercial proposition for deployment in developing countries.

The diseases are then categorized according to which IVR activity will be most beneficial: (watchful waiting, developing or facilitating).



**For Leishmaniasis and Malaria IVR is both a facilitator and a developer

10 May 2004

As developer IVR directly supports and sponsors the development of specific vaccine candidates. IVR is a developer for vaccines against diseases such as malaria, leishmaniasis or measles. As a facilitator, in instances where there are many other parties involved in one capacity or another, IVR is an independent, objective process consultant and strategic or technical adviser for ongoing global research and product development. IVR is a facilitator for work on vaccines against diseases like HIV/AIDS, tuberculosis, dengue and *S. Pneumoniae*. IVR's third role is monitoring. The diseases in this group may well move to either of the other two categories as the global vaccine R&D pipeline develops, and partnerships strengthen. Examples of these diseases are caliciviruses, cholera, typhoid fever, Buruli ulcer and schistosomiasis.

2002-2003 Activity Report

This report covers vaccine R&D activities conducted by IVR during the 2002-2003 biennium in the following disease areas:

Malaria, HIV/AIDS, Tuberculosis, Rotavirus, Shigella and ETEC diarrhoeal diseases, Pneumococcus pneumonia, Meningococcal meningitis, Measles, Dengue, Japanese Encephalitis, SARS and HPV.

Results obtained in the area of New Delivery Systems and Capacity Building for Good Clinical Practices (GCP) and Bioethics are also presented.

Work in 2002-2003 was made possible by support from (in alphabetical order) Belgium, CIDA Canada, Denmark, Finland, France, the Bill & Melinda Gates Foundation, GAVI, Germany, the International AIDS Vaccine Initiative (IAVI), the International Vaccine Initiative (IVI), Ireland, Italy, the Jackson Foundation, Japan, Luxembourg, the Kingdom of the Netherlands, Norway, the Programme for Appropriate Technology in Health (PATH), the Rockefeller Foundation, Sweden, UNAIDS, the United Kingdom, the US Agency for International Development (USAID), the US Centers for Disease Control (CDC), the US National Institutes of Health (NIH), the World Bank.

Malaria Vaccines

FOCUS

More than 2 billion people or 40% of the world s population live in malaria endemic regions. WHO estimates that there are 300-500 million clinical malaria cases annually, making malaria the most prevalent parasitic disease. Estimated to cause 1.1 million deaths annually, it is also the most deadly parasitic disease in the world.

There are several categories of candidate vaccines currently being developed against malaria, containing antigens corresponding to the pre-erythrocytic, blood-stage or sexual stages of the parasite.

Activities and Achievements 2002-2003

Research and product Development

WHO and the UNDP/World Bank/WHO *Special Programme for Research and Training in Tropical Diseases* (TDR) have worked together during 2002-2003 to support malaria vaccine research and development as follows:

- A Phase I clinical trial of a promising blood-stage vaccine candidate *Plasmodium falciparum* chimeric protein (PfCP-2.9) was initiated in Shanghai, China in August 2003.
- Pre-clinical development of four blood-stage vaccine candidates based on the merozoite surface protein-1 (MSP-1) antigen was supported, as well as that of a recombinant EBA-175 protein.
- Several antigen discovery projects were funded.

Vaccine-related activities

- Clinical trial monitoring visits in Shanghai's Changhai Hospital in order to prepare for the Phase I trial described above, assessment visits and good clinical practice (GCP) training.
- Independent monitoring of clinical trials conducted by collaborating organizations.
- Organization of a scientific meeting of African malaria vaccine researchers in conjunction with a meeting of the WHO Malaria Vaccine Advisory Committee (MALVAC) in Maputo, Mozambique in November 2003.
- Publication on the IVR web-site of the global portfolio of malaria vaccine candidates with their current status of development.
- WHO has been appointed as the focal point for an informal grouping of major malaria vaccine funding agencies. This sharing of information and updates on malaria vaccine development efforts by each agency will hopefully promote targeted research activities - closing some of the knowledge gaps in malaria vaccine development.

Objectives and Targets for 2004-2005

Although malaria remains a chronically under-funded disease, public awareness is increasing. There has been unprecedented collaboration among public and private agencies and institutions, plus scientific advancements allowing improved process development of vaccine candidates and development/testing of novel vaccine formulations. WHO will continue to support research and clinical development of selected vaccine candidates as well as to provide normative functions according to guidelines for good laboratory practice (GLP), good manufacturing practice (GMP) and good clinical practice (GCP). This will include capacity building for ethical conduct of clinical trials and providing guidance and independent monitoring of vaccine trials.

Specific activities will be implemented with the following milestones as indicators.

In 2004

- Standardization is completed of Standard Operating Procedures for primate models for screening candidate malaria vaccine antigens.
- New research into improved immune correlates of protective immunity is initiated (WHO contribution: support for selected research projects).
- At least one new malaria vaccine clinical trials site is upgraded to perform according to GCP level.
- A PfCP-2.9 Phase I clinical trial is completed and the results are submitted for publication (WHO contribution: sponsoring of the clinical trial and design of the clinical development strategy)
- A registry is established of malaria vaccine trials sites by region and capacity (in collaboration with other malaria vaccine funding agencies).
- Minimum criteria are set for a site to conduct malaria vaccine trials.

In 2005

- At least one immune assay useful in the selection of candidate antigens/ epitopes is standardized (WHO contribution: support to selected research projects).
- Two Phase I and one Phase II clinical trials start (WHO contribution: continued support of vaccine candidates into clinical trials).
- Clinical trial sites readied for efficacy trials (WHO contribution: support for GCP training).
- Phase IIa standard model protocol for conduct of malaria vaccine efficacy trials available (in collaboration with other malaria funding agencies).

HIV/AIDS Vaccines

FOCUS

With more than 14 000 new HIV infections occurring every day, 95% of them in developing countries, a safe, effective and available HIV vaccine is the best long-term hope for the control of the pandemic, complementing other HIV prevention interventions. Since the first HIV candidate vaccine was clinically tested in 1987, more than 40 different products have been evaluated in approximately 80 Phase I/II trials, 28 of them conducted in developing countries.

From the three large scale Phase III trials conducted thus far, two were implemented in a developing country. WHO, in close collaboration with UNAIDS, has provided continuous guidance and coordination to the international effort to develop and evaluate HIV vaccines. Several countries have WHO-UNAIDS sponsored National AIDS Vaccine Plans, and a WHO-UNAIDS sponsored African AIDS Vaccine Programme (AAVP) is being developed in collaboration with multiple international partners. Although WHO is not directly involved in the development of candidate vaccines, WHO-UNAIDS serves as neutral broker between agencies, industry and host countries and communities, to ensure that vaccine research is conducted with the highest scientific and ethical standards.

Activities and Achievements 2002-2003

The HIV Vaccine Initiative (HVI), a joint initiative of WHO and UNAIDS was established in January 2000 and has constituted one of the technical units of IVR since January 2002. HVI draws significant resources from competencies available within the Department of Immunization, Vaccines and Biologicals (IVB), especially in the domains of quality, regulation and economics. The mission of HVI is to promote the development, facilitate evaluation, and address future availability of preventive HIV vaccines, with a focus in developing countries.

HVI activities follow a strategic plan consisting of four major components:

- *Advocacy, guidance and co-ordination* of the international HIV vaccine effort.
- *Promoting the development of appropriate vaccines* for developing countries. This work has been conducted mostly through the WHO-UNAIDS Network for HIV Isolation and Characterization.
- *Facilitating the conduct of vaccine clinical trials in developing countries* through training and capacity building. For example, the recently launched *AAVP*.
- Working towards *future access and availability of HIV vaccines*.

HVI activities are implemented in close collaboration with partners in industrialized and developing countries.

Advocacy, Guidance and Co-ordination

The development of a safe, globally effective and affordable HIV vaccine, which can effectively complement the existing strategies for HIV/AIDS prevention, is considered the best long-term hope for the future control of the HIV/AIDS pandemic. HVI has maintained a high level of information exchange and advocacy to promote international co-operation and collaboration in the area of HIV vaccines by:

- Facilitating intense policy dialogue and organization of satellite workshops on various aspects of HIV vaccine development at international, regional and national levels.

- Continuous interaction with key partners: agencies, industry, host countries and donors (European Commission, US National Institutes for Health, the International AIDS Vaccine Initiative, Agence Nationale de Recherches sur le SIDA (France), CIDA/Canada, SIDA/SAREC (Sweden), Bill & Melinda Gates Foundation and others).
- Supporting two advocacy projects on community participation, legal and human rights (Canadian Legal Network and the AIDS Vaccine Advocacy Coalition (AVAC).
- Monitoring, analysis and dissemination of information, resulting in 19 technical publications in leading scientific journals over the past two years.

The HIV Vaccine Advisory Committee has provided continuous technical advice to WHO, UNAIDS and Member States on the definition of a global strategy to promote the development of HIV vaccines with a special emphasis on developing countries, as well as by reviewing and providing comments in relation to protocols of clinical trials there.

Promotion of Vaccine Development

- Through the WHO-UNAIDS Virus Network an international collection of HIV vaccine-related reagents has been maintained and widely distributed among academic institutions and pharmaceutical industries. In 2002-2003, over 450 samples were distributed.
- The WHO-UNAIDS Network facilitated comparative evaluation and standardization of various laboratory methods for virus isolation and detailed genetic, biological and immunological characterization. As a result, comprehensive WHO-UNAIDS *Guidelines for HIV Isolation and Characterization* (2nd edition) were developed and published in 2002.
- To ensure the transfer of appropriate laboratory technologies relevant to HIV vaccine research and clinical trials to developing countries, HVI sponsored seven regional training workshops on characterization of HIV strains and immune responses. As a result more than 150 scientists from Africa, Latin America, Asia and Eastern Europe have been trained in the application of these modern laboratory techniques.
- To facilitate the appropriate scientific, regulatory and ethical standards for the conduct of clinical trials in developing countries, HVI in collaboration with other WHO units, convened two expert consultations. These made recommendations with regard to regulatory aspects in HIV vaccine development with a special focus on the needs of National Regulatory Authorities in developing countries and supported targeted training of selected experts from developing countries at a regional workshop.

- A policy statement was developed with AAVP on trials with candidate vaccines corresponding or not to the HIV genotype prevalent in the country where trials take place. This should facilitate review and approval of clinical trial protocols in developing countries.

Facilitation of Clinical Trials

- A major target in this area has been the development of the African AIDS Vaccine Programme (AAVP), a network for African scientists and communities to promote and facilitate HIV vaccine research and evaluation through capacity building and promotion of regional and international collaboration. The AAVP advocates and supports a coordinated effort to contribute to global HIV vaccine development, ensuring that appropriate vaccines are developed and made accessible in Africa. AAVP activities are guided by specific milestones with an overall goal of facilitating the conduct of all stages of clinical trials in Africa over a ten-year period. As a result of its activities, AAVP has received broad recognition and financial support from various international donors.
- HVI continued providing technical and targeted financial support to countries for the development of their National AIDS Vaccine Plans or Strategies (14 countries in total). These define overall national policies and frameworks, as well as plans to develop national infrastructures and capacity, ensuring the appropriate scientific and ethical standards of HIV vaccine-related research and clinical trials.
- Through extensive consultation with all relevant parties and community representatives HVI has facilitated the development of different policies in relation to HIV vaccine trials with a focus on developing countries. In September 2003, HVI in collaboration with UNAIDS, initiated a policy consultation process with regard to standard of care in HIV preventive research.

Future Access

To stimulate HIV vaccine development and to address issues in relation to future access and public health use of eventually successful HIV vaccines, HVI has promoted and supported a number of baseline activities, including:

- WHO-UNAIDS-CDC Technical Consultations on the implications of results from ongoing and planned Phase III efficacy trials in US and Thailand. Development of mathematical models for the development and assessment of public health strategies in relation to the introduction of HIV vaccines. Development of tools **and ways to assess delivery capacity and cost of selected vaccination strategies.**
- An international collaborative pilot study was conducted on delivery and cost effectiveness of future HIV vaccines in 3 countries (Brazil, Kenya, Thailand), plus recommendations for public health use of first generation HIV vaccines.

Objectives and Targets for 2004-2005

For the next biennium, HVI will continue its activities in the same four areas with the following milestones as indicators. These activities will give due attention to the new proposed Global HIV Vaccine Enterprise, to ensure that WHO and UNAIDS continue to provide the necessary global leadership and brokering on this new phase of increased international collaboration on HIV vaccine R&D:

In 2004

- The advocacy strategy plan for HIV vaccine and the WHO-UNAIDS HIV Vaccine Initiative is completed.
- At least two candidate vaccines Phase I/II trials are initiated in developing countries. (WHO-UNAIDS contribution: technical advice)
- The relationship of HVI with the new HIV Enterprise is established.

In 2005

- At least one Phase III trial is launched in industrialized and developing countries, taking advantage of HVI. (WHO-UNAIDS contribution: strengthening sites in Africa, protocol review, and scientific oversight of trials sponsored by the HIV Vaccines Trials Network (HVTN)
- At least five HIV vaccine candidates Phase I/II trials are initiated in developing countries, in collaboration with WHO-UNAIDS. (WHO-UNAIDS contribution: technical advice)
- A credible estimation of future demand for HIV vaccines is available and disseminated.

Tuberculosis Vaccines

FOCUS

Substantial progress in genomics and proteomics, immunology and the vaccinology of tuberculosis (TB) has been made in the last few years. This has resulted in the development of prospective TB vaccine candidates including live, adjuvanted subunit, DNA, rationally attenuated *M. tuberculosis* and improved BCG . These have shown promise in preclinical studies. One candidate has entered into human clinical studies and several more are likely to follow in the near future.

WHO acts as facilitator in the area of TB vaccine R&D and provides support to the TB vaccine development process through advocacy, normative support (guidelines, standards/reagents, etc.) epidemiological back-up, health-economic analysis, clinical trial site identification/characterization, and capacity building for infrastructure and research.

Activities and Achievements 2002-2003

Non-clinical TB vaccine research:

- A network of laboratories for testing TB vaccine candidates in non-human primates has been established, comprising 3 laboratories already involved in TB research (Netherlands, Philippines, USA) and two additional ones (China, United Kingdom).
- A consensus protocol for TB vaccine studies in non-human primates has been developed to be published (a) in a WHO document on TB vaccine testing protocols in animals and (b) on the IVR/StopTB 'TB vaccine resources' website.
- Consensus of a 'gold standard' reference vaccine and reference challenge strain of *M. tuberculosis* for TB vaccine studies in animals has been obtained. The US Food and Drugs Administration has prepared these reagents under funding by WHO and will start distributing them in 2004.

Clinical TB vaccine development:

- Potential clinical Phase III testing sites for TB vaccines in Asian high burden countries have been identified (Bangladesh, Philippines). Capacity strengthening activities were initiated in the Philippines.
- A 'generic considerations' document for the performance of early phase clinical trials of TB vaccine candidates was developed. After extensive review this document will be published in 2004.

Advocacy

- A comprehensive TB vaccination model has been developed. This model can predict the potential impact that introduction of different types of new TB vaccines might have on the course of the TB pandemic.
- A TB resources website has been developed. It will go online in early 2004.

Objectives and Targets 2004-2005

In the coming biennium, WHO intends to continue and expand ongoing activities. In the non-clinical area of work, a major focus will be put on standardization and validation of immunologic assays as well as on the development of animal models for regulatory purposes. In clinical research, effort will be put into developing detailed guidance for efficacy evaluation of new TB vaccines, identification of additional potential future trial sites and capacity building for the performance of TB vaccine trials.

One of the important objectives in advocacy will be to provide a convincing economic case for new TB vaccines in high disease burden countries. The following milestones will serve as indicators for the above:

In 2004

- The TB vaccine resources website goes live.
- A monograph on animal models for TB vaccine evaluation is published.
- At least one immunological indicator of vaccine-mediated protection against TB is standardized.
- Guidelines for Phase I and II clinical investigation of a vaccine against TB are published and a directory of potential sites for Phase III trials is developed.
- A TB vaccine impact model is developed and published.

In 2005

- Two clinical sites are ready to start Phase III efficacy testing of a new candidate vaccine against TB. (WHO contribution: strengthening capacity by training and provision of methodology and assays)
- Updated guidelines for BCG characterization are published.
- Two Phase I/II clinical trials of a vaccine against TB are completed. (WHO contribution: provision of protocols, training and capacity strengthening)
- A health economic study for the development of a vaccine against TB is published.

Rotavirus Vaccines

FOCUS

Rotavirus is recognized as the single most important agent associated with severe acute diarrhoeal illness in infants and children worldwide. The international community, including WHO and the Global Alliance for Vaccines and Immunization (GAVI), has prioritized the development of an effective vaccine for use in children in developing countries, due to the reported high death toll associated with this virus infection. WHO s agenda for rotavirus research was established at an international meeting in February 2000, and this agenda has been followed closely over the last years.

Activities and Achievements 2002-2003

Surveillance activities

- Three global networks for rotavirus surveillance and burden of disease studies have been established in developing countries. WHO has supported technically and financially the core programmes in each network, until further funding became available. In addition, a generic protocol for the burden of rotavirus disease and for surveys of the health services utilization has been made available (document WHO/V&B/02.15).
- Surveillance activities in Brazil, Mexico and Venezuela were supported. These form the core countries of the recently created Latin American Rotavirus Surveillance Network, which is now funded by the Children's Vaccine Programme (CVP) and supported by CDC and the Pan American Health Organisation (WHO/PAHO).
- Initial surveillance activities were promoted in Asia through research grants to China, India and Vietnam, which have evolved into the Asian Rotavirus Surveillance Network with additional support and guidance from CDC, CVP and WHO.
- The African Rotavirus Network was established with core funding from WHO. This encompasses nine countries (Botswana, Côte d'Ivoire, Ghana, Kenya, Malawi, Nigeria, South Africa, Tunisia, and Zambia). Each of these networks has generated crucial information on the rotavirus epidemiology and burden of disease and on strain characterization in the regions.

Vaccine-related activities

- Vaccine clinical trial activities were conducted in Brazil, Mexico and Venezuela. These activities included technical support and funding for clinical trial activities as well as for supporting activities, such as intussusception studies and laboratory analyses.
- The Rotavirus Action Plan for Immunization and Development (RAPID) partnership was established for the parallel development of rotavirus vaccine candidates in Africa and Asia. Four vaccine trials were designed and implemented by WHO in collaboration with GlaxoSmithKline in Bangladesh and South Africa. Two of these trials were completed in 2002/3 and the remaining two will be completed in the first half of 2004. The trials are designed to examine issues for infants in the developing world and include questions such as the potential interaction of the rotavirus vaccine with the oral polio vaccine, both being live oral vaccines. RAPID has been successful in conducting these trials in regions of the world previously ignored for traditional vaccine development.

Intussusception surveillance

WHO has led the way internationally in conducting studies to understand the epidemiology and country/region specific incidences of intussusception, especially in developing countries. Firstly, a WHO document entitled "*Acute Intussusception in Young Children*" has been produced (WHO/V&B/02.19). Secondly, WHO has supported studies investigating the incidence, epidemiology and clinical presentation of intussusception in several countries including Australia, Hong Kong, India, Indonesia, Venezuela and Viet Nam.

GAVI-ADIP

GAVI prioritized the need for rotavirus vaccine development and has implemented a specific programme to accelerate its development and introduction. This programme, the Accelerated Development and Introduction Plan (ADIP), was created at the Programme for Appropriate Technology in Health (PATH) in Seattle and is now called the Rotavirus Vaccine Programme (RVP). During 2002-2003, IVR played a significant role in developing the Rotavirus ADIP plan with CDC and PATH and hosted the secretariat of the Interim ADIP until the permanent team was established. WHO remains a strategic partner of the RVP and is involved centrally in the research activities of the programme. These activities include surveillance and burden of disease activities, intussusception surveillance and vaccine clinical evaluation in developing countries. More specifically, IVR assists the strategic priorities of the RVP, and project review and selection. The role of WHO in the RVP activities will grow as regulatory and quality assurance activities become important with the new rotavirus vaccine candidates, and as the potential introduction of a rotavirus vaccine is realized.

Objectives and Targets 2004-2005

During the next biennium, IVR will maintain its role as the international leader and focal point for burden of disease and surveillance activities in the developing world and for the clinical evaluation of the new rotavirus candidates in the developing world. Many of these activities will be conducted in collaboration and partnership with RVP.

In 2004

- Economic and disease burden estimates for rotavirus are available and documented for developing countries (in collaboration with RVP).
- A training curriculum is in place for national regulatory authorities in potential early adopter developing countries to evaluate pre-clinical to clinical transition.
- An expert review and a national consultation are completed for economic and disease burden estimates related to rotavirus; estimates are documented and published (in collaboration with RVP).
- Phase III efficacy trials are ongoing in developing countries (in collaboration with RVP).

In 2005

- The Phase III efficacy trial is ongoing for a second rotavirus candidate vaccine in the developing world (in collaboration with RVP).
- Regulatory pathways are developed for live rotavirus vaccine products.
- Draft recommendations on the production and control of rotavirus vaccine are available.

Shigella Vaccines

FOCUS

Shigellosis is endemic throughout the world. Worldwide there are approximately 164.7 million cases of shigellosis - of which 163.2 million are in developing countries. Each year, an estimated 1.1 million people die from *Shigella* infection, of which an estimated 69% of all episodes and 61% of all deaths occur in children under five years of age living in endemic areas.

Three types of *shigellae* are responsible for bacillary dysentery: *S. sonnei* is classically predominant in industrialized countries (5% of infections in developing countries - 77% in industrialized countries); *S. flexneri type 2a* is predominant in developing countries (60%), and has become increasingly resistant to antibiotics (eg. ampicillin but is still reportedly sensitive to quinolone). Recently, the trend in the *S. flexneri* serotypes has been altered in Bangladesh where *S. flexneri 2b* dominates.

Activities and Achievements 2002-2003

Surveillance activities

- IVR has been a partner of the International Vaccine Institute (IVI) in Seoul, Republic of Korea and has facilitated and supported activities in several Asian countries for the surveillance of Shigella burden of disease and serotype predominance as part of the IVI Diseases of the Most Impoverished (DOMI) project. These activities include sites in Bangladesh, Pakistan and China.
- Studies have investigated the genotype and phenotype of the isolated strains of the Shigella species, which has shown the shift in Bangladesh, for instance, to *Shigella flexneri 2b*. Antibiotic resistance has also been monitored.

Vaccine-related studies

- Studies have been supported in collaboration with the Institut Pasteur, Paris. These studies have evaluated the mutations causing atoxic lipid A in the attenuation of the inflammatory responses of live *Shigella* vaccine candidates.
- Support was provided for the investigation of immune responses to shigellosis in studies conducted at the International Center for Diarrhoeal Disease Research (ICDDR) in Dhaka, Bangladesh.

Objectives and Targets 2004-2005

The status of research towards *Shigella* vaccine lags behind that for other bacterial enteric infections, such as cholera and typhoid fever. Nevertheless, the current prospect has never looked more promising with several academic research institutions working on *Shigella* vaccine candidates. Many of these are now entering clinical trials, or need to be evaluated in clinical trials in humans and will eventually need to be evaluated in clinical settings in developing countries where shigellosis is endemic. IVR will play a strategic and facilitatory role in these activities and will continue the strong collaboration with various research institutions to drive the research agenda forward.

In 2004

- An international technical meeting is organized on the "*Future Needs for Shigella Vaccine Research for Children in Developing Countries*". The meeting report serves as the agenda to focus research activities during the next three to five year period

for *Shigella* vaccines.

- Surveillance activities for *Shigella* burden of disease are initiated in sub-Saharan Africa.
- Surveillance activities and translational studies are ongoing in Asia. (WHO contribution: technical assistance with limited funding support, IVI to co-ordinate and fund activities)
- A live oral attenuated multivalent vaccine is evaluated in a Phase I/II trial. (WHO contribution: technical assistance and funding support; the Center for Vaccine Development (CVD), Maryland, USA will co-ordinate the trial)

In 2005

- A live oral attenuated multivalent *Shigella* vaccine Phase II clinical trial is ongoing. (WHO contribution: technical assistance and possible partial support; CVD will co-ordinate the trial)
- A Phase III trial of an oral live attenuated candidate vaccine (SC602) is ongoing in a developing country. (WHO contribution: technical assistance, IVI will co-ordinate the trial)
- Studies to identify distribution of antibiotic resistance of circulating *Shigella* strains are ongoing in some developing countries. (WHO contribution: to facilitate and offer technical/funding assistance)

Enterotoxigenic Escherichia Coli (ETEC) Vaccines

FOCUS

In community-based studies of children in endemic settings, enterotoxigenic *Escherichia coli* (ETEC) is the most frequently isolated enteropathogen, accounting for approximately 380 000 deaths annually. The peak of incidence of ETEC diarrhoea in these settings occurs in the first year of life, with a declining incidence with age thereafter.

In children, the tendency of ETEC to cause dehydrating diarrhoea is less (approximately 5% of episodes) than that for rotavirus (approximately 36%). However, because the incidence of ETEC diarrhoea is considerably more common than rotavirus diarrhoea in children, the absolute number of dehydrating diarrhoea episodes due to ETEC is around 70% of the number of such episodes due to rotavirus. In addition, unlike rotavirus, ETEC diarrhoea in children has been associated with subsequent growth faltering.

Activities and Achievements 2002-2003

Surveillance

- Support has been given to facilitate studies investigating the burden of disease in young children in developing countries. In particular two studies have been supported in Egypt and in Bangladesh, which have shown a high burden of disease due to this infection.
- Studies supported by WHO have investigated the genotype and phenotype of the isolated strains of ETEC.
- Studies conducted in Guatemala have focused on the distribution of ETEC strain markers in travellers when compared to children living there.

Vaccine-related studies

- Both technical support and funding was contributed to a Phase II ETEC vaccine trial in Egypt to investigate the co-administration of the killed ETEC vaccine candidates (rCTB-CF ETEC) with the routine childhood vaccines.
- Technical advice and partial funding was contributed to a second study conducted in Egypt and investigating the protective efficacy of the killed ETEC vaccine.
- Pre-clinical studies were supported at the Center for Vaccine Development (CVD), Maryland USA examining the potential of an oral, live, attenuated, multivalent ETEC/*Shigella* vaccine candidate.

Technical meeting

- An international technical meeting was convened in September 2003 entitled *"Future Directions for Research on ETEC Vaccines for Children in Developing Countries"*. It was the first international meeting to be convened since 1996 in the field of ETEC and was attended by the significant researchers and multinational companies involved in ETEC vaccine research. A series of recommendations arose from this meeting. These will set the future agenda, stimulate further research in this arena and will form the basis of future WHO activities.

Objectives and Targets 2004-2005

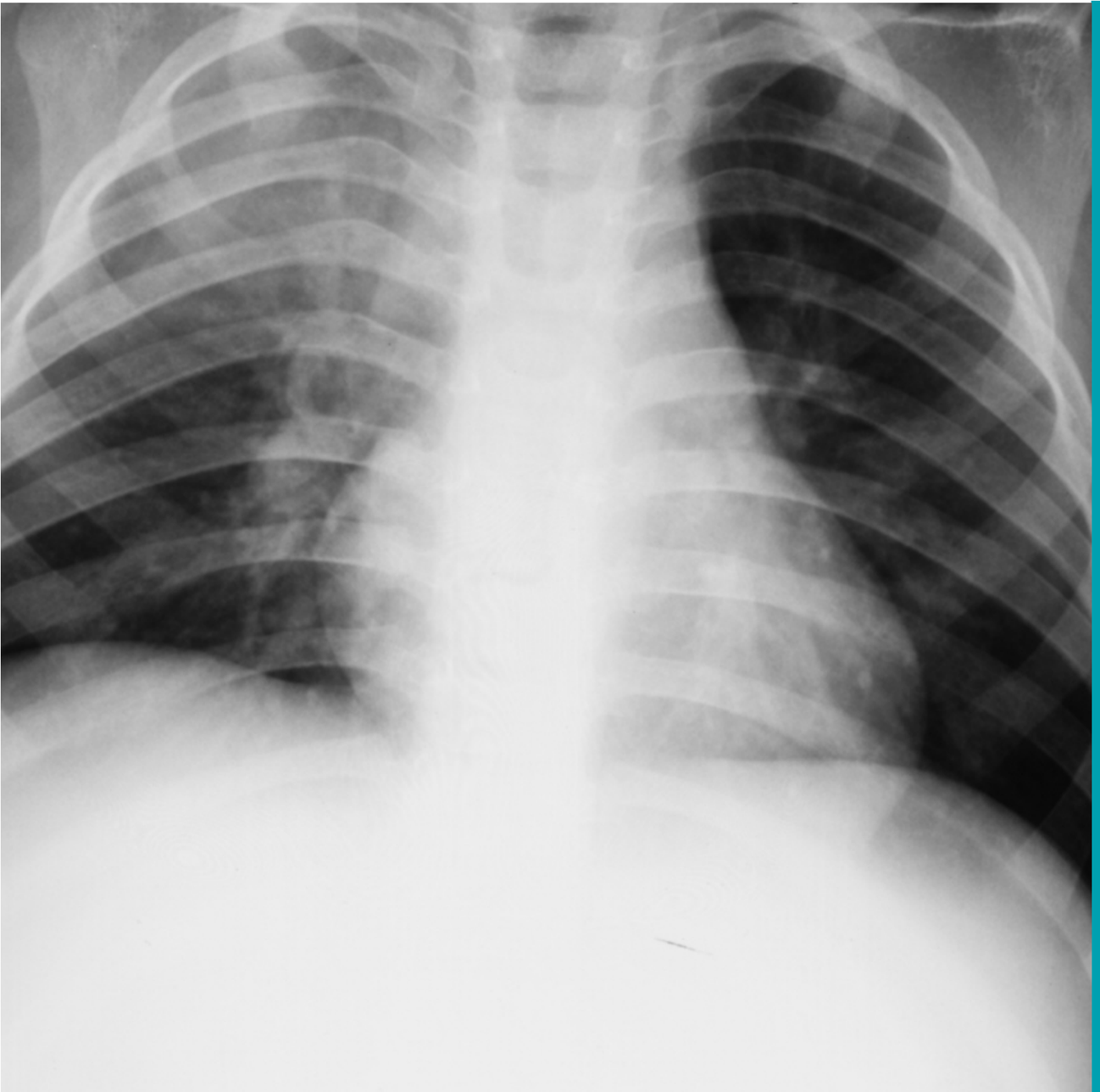
During 2004-2005, IVR will adopt the recommendations that have originated from the WHO Technical Meeting and develop a strong programme designed to accelerate the development and clinical evaluation of ETEC vaccines for children in the developing world. Currently, this programme is driven by IVR and no single significant additional partner is committed to these activities. Provided adequate funding can be secured, the following milestones should serve as a roadmap for research activities in 2004-2005.

In 2004

- Surveillance activities for ETEC burden of disease are initiated in sub-Saharan Africa and Asia.
- A clinical trial to evaluate the killed ETEC vaccine is initiated in a developing country. (WHO contribution: technical advice and partial funding to ICDDR, Bangladesh in collaboration with Göteborg University)
- An oral, live attenuated vaccine is evaluated in a Phase I/II trial by CVD. (WHO contribution: technical advice to CVD)

In 2005

- Adult volunteer studies are ongoing to evaluate proof of principle of the immunological and potential protective role of specific colonization factors (CFs). (WHO contribution: technical assistance)
- Studies to identify distribution of important CFs are initiated in some developing countries. (WHO contribution: support for selected projects)
- An oral live attenuated vaccine Phase II clinical trial is ongoing. (WHO contribution: technical assistance and partial funding)



Pneumococcal Vaccines

FOCUS

Globally, pneumonia remains a major cause of childhood mortality, accounting for approximately 2 million deaths annually. Most deaths are caused by bacterial pneumonia, with *Streptococcus pneumoniae* a predominant pathogen. A pneumococcal polysaccharide vaccine has been available for several years but its effectiveness is limited by its inability to induce immunological memory and its poor immunogenicity in infants and young children.

A 7-valent pneumococcal conjugate vaccine was recently licensed in several industrialized countries, but lacks some serotypes that are important in developing countries. WHO focus is on developing the evidence that will enable rational decision for the introduction and use of the vaccine in developing countries.

Activities and Achievements 2002-2003

Surveillance activities

- WHO has supported continued surveillance for invasive pneumococcal disease and pneumonia in two populations with high burden of disease where pneumococcal vaccine trials were conducted. These studies will generate data on the duration of protection (in HIV infected and uninfected children) and the effectiveness of the vaccine in these populations.
- A study to estimate the burden of radiologically confirmed pneumonia was initiated in Mozambique. The study uses the same definitions and methods for identifying pneumonia cases, which will allow the application of vaccine trial data to determine the potential impact of pneumococcal vaccine on bacterial pneumonia in Mozambique.

Clinical development

- Enrolment was completed for the efficacy trials in the Gambia and the Philippines. WHO is a co-sponsor of the Gambia trial and provides technical assistance to the Philippines trial, and supports the Data Safety Monitoring Boards (DSMB).
- One study evaluating the safety and immunogenicity of a neonatal dose and two evaluating alternative vaccination schedules of pneumococcal conjugate vaccine were initiated.
- A study on the immune response of pneumococcal conjugate vaccines in HIV infected infants was completed.

Vaccine-related activities

- The main interest in pneumococcal vaccine development is its potential to reduce pneumonia mortality, yet there was no commonly accepted standard for defining this key outcome in vaccine trials. In 2002 WHO completed the process of developing a standard process for categorising radiological pneumonia along with a training and quality control programme. Data from the three trials that used this process became available in 2003, while other trials and disease burden studies are ongoing.
- Guidelines for the production and quality control of pneumococcal conjugate vaccines and serological criteria for the evaluation of these vaccines in infants and children were defined. These will facilitate registration of new vaccine formulations and combinations.
- Standard methods for the collection, storage and testing of nasopharyngeal specimens in pneumococcal vaccine trials were published.

GAVI-ADIP

- WHO participated in the development of the Pneumococcal Accelerated Development and Introduction Plan (ADIP) that was approved in June 2002. It acted as the secretariat for the interim ADIP activities before the selection of the host institution (Johns Hopkins University, Baltimore, USA), during which period proposals for support to ongoing vaccine trials and surveillance networks were advertised, reviewed and ranked. WHO is a strategic partner of the pneumococcal ADIP and a Memorandum of Understanding has been signed between both parties.

Objectives and Targets 2004-2005

During the next years, IVR intends to support the development of pneumococcal vaccines both in collaboration with the pneumococcal ADIP and independently when it identifies gaps and areas where WHO has a comparative advantage. Research activities will be undertaken in various areas: surveillance, clinical evaluation, economic analyses, standardization and guidelines, regulation and new licensing pathways. The following milestones will serve as indicators for the above.

In 2004

- At least four networks for laboratory-confirmed pneumococcal disease are established in developing countries. (WHO contribution: technical assistance. Funding for networks through ADIP)
- Initial data are available from the Mozambique study to determine the appropriateness of a generic protocol to measure the burden of pneumonia in developing countries (in collaboration with the Children's Vaccine Programme (CVP).
- The initial phase of an evaluation of the safety of a neonatal dose of pneumococcal conjugate vaccine is completed.
- The standardization and validation of serological assays to measure immune responses for pneumococcal conjugate vaccines are completed and conclusions published.
- The two-year post-vaccine introduction surveillance is completed in at least one developing country site and in one high-risk indigenous population.

In 2005

- Pneumonia disease burden data (using standardized WHO radiological definitions of pneumonia) are available from Mozambique and at least one other developing country (in collaboration with CVP).
- An efficacy study of pneumococcal conjugate vaccine with radiological pneumonia as an end-point is completed in the Gambia and the Philippines (in collaboration with other partners).
- A study evaluating the safety and immunogenicity of a neonatal dose of pneumococcal conjugate vaccine is completed in Kenya.
- Advisory groups to determine optimal vaccination schedules for pneumococcal vaccines are established in three regions.
- Regulatory pathways in principle are available for all pneumococcal vaccines at the clinical stage, including regulatory oversight to ensure quality and consistency at international level and appropriate epidemiological analysis of clinical data.
- Acceptable production sources are identified for this product, ensuring that developing country markets have access to the vaccine.

SARS Vaccines

FOCUS

Severe Respiratory Syndrome (SARS) was first detected in 2002 when it started its rapid regional spread in several Asian countries and to North America, Europe and Australia. With leadership from WHO and its Regional Office for the Western Pacific, national authorities of affected countries have been successful in mounting an effective response, which resulted in control and curtailing this epidemic. However, it remains unclear whether the SARS epidemic can re-emerge in the near future, and it is therefore important to maintain a high level of alert of the global surveillance and control systems,

as well as to promote the development of additional tools that could complement and improve the existing SARS control measures. This includes the development of safe, globally effective and affordable vaccines against SARS, which was also emphasized in the World Health Assembly Resolution on SARS in May 2003 (WHA56.29).

Over the past year, basic science has made an enormous progress in identification of a new human Coronavirus as an etiological agent of SARS. This is an important step towards to the development of a SARS vaccine.

Activities and Achievements 2002-2003

- To explore the potential role of WHO in promoting the development of a SARS vaccine, IVR has convened a large international consultation, involving the leading experts in SARS virology, immunology, pathogenesis and animal models, representing both public health institutions, academia and the pharmaceutical industry. The meeting resulted in a number of recommendations with regard to:
- Scientific aspects that need to be investigated to guide safe and rational development of SARS vaccines;
- Needs for international collaboration, including collaboration with research agencies, countries and pharmaceutical industry;
- Needs for the development of regulatory and biosafety guidelines in relation to SARS vaccine development;
- Provision of support to the national vaccine programmes and regulatory authorities involved in SARS vaccine research.

Objectives and Targets 2004-2005

To follow up these recommendations, IVR is planning to further elaborate on specific activities that would need to be coordinated and partially supported by WHO. Activities undertaken in 2004 will be evaluated against the following indicators. The level of activity in 2005 will be partially dependant on the occurrence of a new SARS epidemic.

In 2004

- A workshop is organized on "*Animal Models for the Development of SARS Vaccines*".
- In collaboration with the WHO Regional Office for the Western Pacific and the WHO Office in China, a fact-finding mission is conducted to the People's Republic of China. The major objective of this mission will be to identify potential areas of collaboration between WHO and China and develop a jointly supported plan of activities.
- The safety/immunogenicity Phase I trials of inactivated SARS vaccines are initiated. (WHO contribution: technical advice and support).

In 2005

- WHO recommendations and guidance documents in relation to regulatory aspects and biosafety in SARS-related research and clinical trials are made available.

Japanese Encephalitis Vaccines

FOCUS

Japanese encephalitis (JE) is an untreatable mosquito-borne viral disease that periodically flares up into major epidemics in Asia. Thirty percent of clinical cases are fatal, and many of those surviving retain permanent neuropsychiatric disabilities. This makes JE a significant public health problem in the region. The only vaccine that is internationally available is an inactivated mouse-brain-derived product that is not scaleable to meet actual needs.

A live-attenuated vaccine produced and widely used in China does not yet fulfil international regulatory standards. Hence, there is a need for vaccines that are safe, efficacious and scaleable to public health use in endemic countries.

New generations of JE candidate vaccines are being developed, including one which uses the yellow fever vaccine as a vector for JE envelope sequences, which has shown to be very immunogenic in Phase I trials. WHO's role is to continue facilitating the clinical evaluation of novel JE candidate vaccines, with a view to introducing better products into the national immunization programmes.

Activities and Achievements 2002-2003

Efficacy of JE vaccines against JE viruses in different regions

- Detailed studies have been supported on the immune responses elicited by existing inactivated vaccine against several circulating JEV genotypes (I-IV), confirming that JE vaccines containing a single serotype of virus are likely to protect against all circulating viruses.

Standardize assays and establish reference materials

- A repository of well-characterized standard reagents and reference materials has been established, which includes JEV virus strains, cell banks and standard sera.
- The development of Standard Operating Procedures for assays has been initiated.

Support a second generation vaccine adapted to developing country needs

- WHO is actively supporting the development of a second-generation live-attenuated JE vaccine that is rationally constructed on the backbone of a yellow fever (YF) vaccine. This candidate has proven to be safe and immunogenic in Phase II clinical studies, and now awaits evaluation in disease-endemic countries. WHO has signed a Memorandum of Understanding with the commercial vaccine developer with the goal of testing and making the vaccine available to endemic developing countries.

Objectives and Targets 2004-2005

During the next biennium, IVR will continue and expand on ongoing activities, with the following milestones as indicators.

In 2004 • The evaluation is completed of the safety and immunogenicity (Phase I/II) of YF/JE chimeric vaccine in adults in a country in the Western Pacific Region (WHO contribution: technical advice and support).

In 2005 • Paediatric Phase I/II evaluation of the YF/JE chimeric vaccine is initiated in at least one developing country (WHO contribution:technical advice and support, in collaboration with various partners).

Dengue Vaccines

FOCUS

Dengue viruses have dramatically spread through the world, causing an estimated 50-100 million cases of dengue fever (DF) and 500 000 cases of the life-threatening dengue haemorrhagic fever (DHF) every year. Current vaccine development efforts are targeted to produce tetravalent candidate vaccines, with the first generation vaccines being empirically attenuated through cell passage.

A second generation of live attenuated vaccines is being developed using molecular approaches, such as using attenuated-deletion mutants of dengue virus, or the yellow fever vaccine as a vector for dengue envelope sequences.

Dengue vaccines currently in the pipeline have proved immunogenic and safe in clinical trials, and the conduct of efficacy trials can be foreseen for the near future. Of special importance is the need to assess carefully the potential risks associated with immune enhancement of DHF. IVR intends to collaborate closely with the newly established Paediatric Dengue Vaccine Initiative (PDVI).

Activities and Achievements 2002-2003

Research on mechanisms of protection and immunopathogenesis

- Protective neutralizing antibodies induced by vaccination with live tetravalent vaccine have been characterized in detail in a project funded by WHO.
- A dengue virus human challenge protocol has been established. This study will yield a fine-characterization of the humoral response and its protective capacity.
- WHO-supported studies to assess the role of pre-immunity to other flaviviruses on vaccine-induced immune responses, leading to a better understanding of protective versus pathogenic immune responses.

Standard reagents and laboratory methods

- The establishment of a dengue standard reagent bank has been completed, which includes reference sera, viruses and cell banks. A second repository of reference and working materials will be established in Thailand, which will allow easier shipment of materials to collaborators in the region. This facility is being established as a WHO reference laboratory on dengue and Japanese encephalitis.
- The drafting of a standardized protocol for the evaluation of Dengue vaccines in monkeys has been initiated.

Facilitation of clinical research

- A Task Force in support of ongoing vaccine clinical trials has been established as a joint effort between PDVI and WHO. This group reviews progress in vaccine trials and facilitates the development of dengue vaccines through targeted activities. Recently, the group has reviewed the draft WHO guidelines for the production and quality control of life-attenuated Dengue vaccines.
- Financial support has been given by WHO to Mahidol University to build up capacity and infrastructure to conduct clinical trials.

Objectives and Targets 2004-2005

During the next biennium, IVR will continue and expand ongoing activities, with the capacity to reach the following milestones intended to measure progress:

In 2005

- A standardized protocol is developed for evaluation of vaccines against dengue in monkeys. (WHO contribution: funding to the project)
- Studies are completed on the mechanism of immune enhancement and neutralization escape. (WHO contribution: support to selected research projects)

In 2004

- A cohort is prepared for Phase III trials of tetravalent dengue vaccine in a developing country. (WHO contribution: technical advice)
- Criteria to assess vaccine long-term safety will be developed.

Human Papillomavirus Vaccines

FOCUS

About 500 000 cases of cervical cancer occur each year worldwide, and 80% of cases affect women living in developing countries, where cervical cancer is the foremost cause of cancer mortality among women. Sexually transmitted Human Papillomavirus (HPV) has been established as the major cause of cervical cancer, and therefore vaccines to prevent the viral infection have the potential to prevent cancer.

Research institutions in the public and private sector are developing prophylactic candidate vaccines, among which those based on recombinant L1 viral capsid proteins of HPV types 16 and 18 (VLPs) are the most advanced. Upon injection these candidates induce neutralizing antibodies that appear to prevent papillomavirus infections and related diseases. The public sector is giving special attention to accelerate the development, availability and introduction of prophylactic HPV vaccines in developing countries where they are most needed, where other diagnostic and therapeutic options are often not affordable, not implemented or simply unavailable.

Activities and Achievements 2002-2003

- A comprehensive plan to accelerate the development and introduction of HPV vaccines in developing countries has been developed.
- A number of potential collaborations/partnerships with both the public and private sector were explored.
- Areas for conducting vaccine clinical trials were identified and selected countries visited (India, Philippines and Korea) in order to provide information and start discussions on trial design and future vaccine use.
- A review and update of existing and ongoing studies on HPV type-specific cancer prevalence worldwide have been conducted in collaboration with the International Agency for Research on Cancer (IARC).
- Data on manufacturing costs of current HPV vaccine candidates were generated and alternative possibilities for improved, less costly production explored.
- An assessment of selected developing country manufacturers capacity was completed.
- International reference reagents for HPV DNA and antibody detection assays were developed.
- Meetings on endpoints for clinical studies relevant to developing countries were convened.

Objectives and Targets 2004-2005

A number of activities are planned to continue the implementation of some of the above-mentioned projects. The following milestones will provide indicators to measure success.

In 2004

- An analysis is conducted of the acceptability and feasibility of HPV vaccination in developing countries. (WHO contribution: paired efforts with external partners, like the Program for Appropriate Technology in Health (PATH)).
- The cost-effectiveness modelling of HPV vaccination in Asia and Africa is completed. (WHO contribution: support for two studies)
- A country-specific online database is elaborated on HPV and cervical cancer burden (in collaboration with IARC).

In 2005

- At least two novel HPV vaccine candidates are pre-clinically tested. (WHO contribution: joint support with the US National Cancer Institute (NCI))
- Studies on HPV type prevalence are conducted in selected Asian and African developing countries with high disease burden and which lack this information (in collaboration with IARC).

Meningitis Vaccine Project

FOCUS

African meningitis belt countries suffer from endemic meningococcal disease - primarily in children under the age of five years. In addition, serogroup A meningococcal disease occurs in explosive epidemics predominantly throughout what is known as the meningitis belt of sub-Saharan Africa. Epidemics are mostly caused by serogroup A strains, although serogroup C strains have also been responsible for outbreaks. Recently, resurgence of serogroup W135 has also caused concerns.

The African belt of epidemic meningitis

A vaccine that can provide long-term protection in children (routine immunization) and adults ("catch-up" strategy), that can be administered at the same time as other routine vaccinations and that significantly reduces carriage could prevent epidemics and eliminate the need for emergency interventions. There are good reasons to believe that a serogroup A meningococcal conjugate vaccine could do just that, but serogroup A meningococcus is unusual in industrialized countries and therefore vaccine manufactures did not foresee a profitable market.

A new approach was needed to deal effectively with the public health problem of epidemic meningococcal disease in sub-Saharan Africa. To this end the Meningitis Vaccine Project (MVP) was created as a partnership between WHO and the Program for Appropriate Technology in Health (PATH). The Bill and Melinda Gates Foundation has provided support for this project which started with WHO funds.

Activities and Achievements 2002-2003

Development of a new conjugate vaccine

- A comprehensive ten year workplan for the project was developed by WHO and PATH, including budget needs and a monitoring strategy.
- Extensive contacts with vaccine manufacturers were established and pursued and different models for product development explored.
- Two different product development plans were explored for final selection in 2004.
- Sources of raw materials for the conjugates were secured and clinical-grade material prepared.
- Clinical development plans both for 1-29 year olds and under ones were developed, including different scenarios.
- Site visits to seven African field sites for clinical studies were conducted and their capacity assessed.

Strengthening of epidemic meningitis surveillance

- Efforts to strengthen epidemic meningococcal disease surveillance were initiated to help describe serogroup distribution in the region, as well as disseminate issues related to vaccine development, timely detection of the disease and epidemic response in the African meningitis belt. With epidemic Nm W135 disease during 2001-02 in Burkina Faso, focus was on the integration of timely laboratory confirmation into surveillance activities.

Epidemiological information on epidemic meningitis

A comprehensive review of the epidemiology of meningococcal meningitis in sub-Sahara Africa over the last decade was initiated. A precise scope of work was outlined and the following steps taken:

- A relational database was developed to receive the information.
- Contacts were established with all potential contributors to this effort including WHO experts and collaborating centres, research centres and laboratories, public health officials, and vaccine manufacturers.

Objectives and Targets 2004-2005

- Regional and national epidemic meningococcal disease surveillance systems are strengthened and expanded to evaluate the importance of serogroup W135 as a potential epidemic strain in African meningitis belt countries.

In 2004

- Serological assays to measure immune responses for serogroup A meningococcal conjugate vaccine are standardized and validated.
- A forecasting demand model for this vaccine is drafted in collaboration with countries, and communicated to the manufacturer to ensure adequate production capacity. (WHO-MVP milestone)
- Specifications and quality control procedures of serogroup A conjugate vaccine are completed based on the recommendations established for serogroup C conjugate vaccine.
- A GMP batch of a conjugate meningococcal vaccine is produced and quality-controlled. (WHO-MVP milestone)
- A comprehensive overview of past and actual meningococcal meningitis situation in African target countries, including the assessment of serogroup W135 as a potential epidemic strain is generated. (WHO-MVP milestone)

In 2005

- A regional-based plan for meningococcal conjugate vaccine introduction is drafted with WHO's Regional Offices for Africa and the Eastern Mediterranean. (WHO-MVP milestone)
- A Phase I safety and immunogenicity study (healthy adult volunteers) of serogroup A meningococcal conjugate vaccine is completed in the producing country. (WHO-MVP milestone)
- A financing plan for A conjugate vaccine is agreed in target countries. (WHO-MVP milestone)

New Vaccine Delivery Systems (NVDS)

FOCUS

In general, IVR s activities in the area of new vaccination approaches have included identifying novel technologies to either improve the immunogenicity or the delivery of vaccines, prioritizing them, and providing seed money for research that could lead to the development of formulations of particular relevance for developing countries.

Recently, a more proactive approach to develop projects in selected priority areas has been initiated.

With the continued help and advice of a Steering Committee of independent experts, technological barriers to improved vaccination logistics and safety are being identified, and specific activities to overcome these barriers conducted. Of particular interest are needle-free vaccine delivery systems including technologies for nasal, oral and transdermal delivery. The aim now is to focus on some of these technologies which can be realistically developed and implemented, and which will have a significant impact.

Activities and Achievements 2002-2003

- The efforts of the New Vaccine Delivery Systems Steering Committee in the area of new technologies for improved and simplified immunization have been re-directed towards focused delivery projects.
- An assay has been developed to measure trace blood contamination on needle-free jet injection devices. This assay is undergoing good laboratory practice (GLP) validation.
- Sugar-glass stabilization technology as a means of increasing the stability of measles vaccine has been evaluated.
- Collaboration on a needle-free delivery of dry vaccines using a novel ballistic delivery system has been initiated.
- A clinical trial protocol to investigate the immunogenicity of a needle-free transcutaneous measles vaccine delivered via a patch was designed.
- In collaboration with GAVI Working Group and the New Technologies Working Group of the GAVI R&D Task Force, a technical analysis and an investment-case analysis for three selected areas of technology was prepared: 1) vaccine stabilization; 2) syringe defanging; and 3) performance monitoring through detection of biomarkers of effective immunization;

Objectives and Targets 2004-2005

In the coming biennium, IVR intends to continue and expand ongoing activities. In the area of improved safety, needle-free delivery will remain a focus. For jet injector evaluation, now that an assay is available to detect possible contamination, WHO will seek advice on the size and endpoints of clinical trials that will be required to establish the safety of the new-generation devices. In addition, to explore the potential for implementing disposable-cartridge jet injectors, WHO will call a meeting of interested parties to evaluate the feasibility of establishing a standard for cartridges, and to evaluate the interest from industry to pre-fill cartridges with vaccines.

The following milestones have been identified as indicators of progress:

In 2004

- A decision is reached on the safety status of multi-dose jet injectors.
- A decision is reached on the development of a projectile/implant (ballistic) subcutaneous delivery system. (WHO contribution: funding and technical support)
- At least one additional needle-free proof-of-principle study (transdermal or nasal) is undertaken.

In 2005

- A Phase I/II trial is completed of a needle-free projectile/implant (ballistic) delivery system.
- Feasibility of implementing cryoprotectants to overcome vaccine freezing is assessed.

Measles Aerosol Project

FOCUS

Measles remains a major cause of morbidity and mortality due to vaccine preventable diseases. Recently, WHO estimated that in 2002 610 000 persons died due to measles. There is a desire for an equally safe, effective and cheap vaccine, which is easier to administer, less invasive and that could been administered by non-medical personnel.

A review of the studies using measles aerosol vaccine indicates that: (a) seroresponse rates in infants and school children after aerosol immunization are at least as good as subcutaneous route; (b) frequency of adverse events following vaccination is lower than with percutaneous route; (c) additional cost benefits could be accrued. The decrease in vaccine dose volume (i.e. up to five times more children could be vaccinated using the same amount of vaccine) and elimination of syringe and needle costs, including disposal, could results in important savings in supplies costs.

Bearing in mind the above, WHO has initiated the *Measles Aerosol Project*. The goal of this project is to license at least one method for respiratory delivery of currently licensed measles vaccines, which will provide a means of administering measles vaccine, which is safer, easier and cheaper than injection.

Work related to the Measles Aerosol Project is performed under a collaborative arrangement between the Centers for Disease Control and Prevention, USA, the American Red Cross and WHO and has received financial support from the Bill and Melinda Gates Foundation.

Activities and Achievements 2002-2003

- A product profile, the project workplan and the regulatory pathway for licensure were developed, toxicology studies were completed and generic clinical trials protocols for the Phase I and II trials were drafted.
- Performance and usability criteria were developed to identify suitable devices to be included in toxicology and clinical trials.
- A meeting with UNICEF Supply Division was held to review the procurement process for measles aerosol devices.
- Animal studies for evaluation of immunogenicity and safety using three different devices are being completed.
- Ad-hoc expert consultations on potential safety concerns (e.g. respiratory concerns, HIV and other vulnerable hosts) and methods for evaluation were held.

Objectives and Targets 2004-2005

During 2004-2005, a major effort will be concentrated on the clinical activities aimed at fulfilling the requisites to complete filing for licensure. In addition, some activities related to the future introduction and use of this vaccine will take place, in preparation of a successful incorporation into immunization programmes. The following milestones will be used to evaluate success:

In 2004

- Preclinical studies to characterize the performance of selected nebulizers and development of criteria on which devices are completed.
- Economic analyses are completed.
- An Investigational New Drug dossier (IND) for Phase I is submitted to Indian regulatory authority (in collaboration with the Serum Institute of India).
- A Phase I clinical study is completed.
- Methods suitable for Phase II clinical trials and likely trial sites are identified.

In 2005

- A clinical protocol for Phase II studies is developed and reviewed.
- An IND for Phase II trial is submitted to Indian regulatory authority (in collaboration with the Serum Institute of India).
- Phase II studies are initiated.

Capacity Building in Good Clinical Practice (GCP) and Bioethics

FOCUS

Once the safety profile of a candidate vaccine has been established in pre-clinical studies, it is necessary to conduct clinical trials in humans to demonstrate both safety and immunogenicity of the product. Further, the protective efficacy of the vaccine should be confirmed in a well-designed clinical trial before licensing for public use.

All these studies should be conducted in agreement with good clinical practice (GCP) standards to ensure the safety of the trial participants, as well as the quality and credibility of data obtained.

The most appropriate clinical trial sites are most often located in regions where disease incidence is high and where the vaccine, if effective, is likely to be used in the future. Therefore, clinical development of new vaccines focuses on developing countries. However, many clinical sites in these regions do not have previous experience in GCP nor the capacity to conduct proper ethical review. As a collaborator or sponsor of vaccine clinical trials, IVR in collaboration with the UNDP/World Bank/WHO *Special Programme for Research and Training in Tropical Diseases* (TDR) is building or strengthening the capacity of selected clinical trial sites to conduct vaccine studies in agreement with the highest GCP and bioethics review standards.

Activities and Achievements 2002-2003

Implementation of GCP standard

- Implementation of GCP standard in vaccine clinical trials sponsored by IVR has been ensured by the quality control process of clinical monitoring. All vaccine trials undertaken in collaboration or under the sponsorship of IVR have been monitored for GCP compliance.
- In collaboration with TDR, the GCP concept has been introduced to a new trial site at Changhai Military Hospital, Shanghai, China for a malaria vaccine Phase I trial. This trial has been monitored and regularly inspected, and seems to attain a satisfactory GCP standard.

Generic vaccine clinical trial protocol

- IVR has developed a generic vaccine clinical trial protocol in accordance with ICH-GCP. This generic document has been produced based on a TDR protocol outline designed for drug studies and is focused on vaccine-specific issues. This should help potential investigators and responsible officers to understand the requirements and information needed for each section of the protocol.

Guidelines for trial site selection

- Draft guidelines for trial site selection have been developed. These guidelines will be used by IVR as a general tool for trial site assessment. For each particular vaccine, a specific scoring for site selection will depend on the specific requirements stated in the protocol.

Objectives and Targets 2004-2005

In 2004

Trial site information database

- A questionnaire is developed to be distributed to researchers who are interested in conducting vaccine clinical trials in collaboration with WHO. The information requested includes trial site location, previous clinical trial experience and GCP training, trial site facilities in terms of personnel, equipment and infrastructure, details about institutional ethical review board or committee and national ethical review board and about other regulatory authority governing clinical trials, as well as on the epidemiology of common diseases in the area (incidence, immunization coverage and immunization programme deployed in the area).

In 2005

Mapping the area for capacity building: GCP and Bioethics

- Based on the information derived from our trial sites' database, areas and countries where GCP or Bioethics training is needed are defined. Potential sites for training are grouped according to geographical location and need for capacity strengthening.

GCP and Bioethics training

- Plans for training on GCP and Bioethics will depend on site requirements, available funding, and links with other units/institution within and outside WHO.

a) GCP training

- Country level training: this is conducted in the context of the specific GCP training undertaken at an institution of that country for a particular clinical trial sponsored by IVR. Other investigators from that country are invited to join during the GCP training sessions. This minimizes costs of travelling and makes the best use of monitoring visits.
- Regional level training: this will be undertaken in the context of GCP training activities conducted for a specific clinical trial in that region. If funding permits, participants from neighbouring countries will be invited to attend the training at the same time. Whenever possible, these activities will be undertaken in collaboration with other units/agencies, like the newly established European and Developing Countries Clinical Trials Partnership (EDCTP). TDR will be IVR's strategic partner for these activities.

b) Bioethics training

- In connection with TDR and the newly established SIDCER (Strategic Initiative for Developing Capacity in Ethical Review) forum, bioethics networks are formed in various regions of the world e.g. FERCAP, PABIN, FLACEIS, FECCIS.

IVR supports investigators or national institutions to attend the regional workshop on Bioethics in order to help them strengthen their own national/institutional ethical review board in the future.

c) Combined GCP and Bioethics training

- In regions where there are many investigators and institutions lacking both GCP experience and Bioethics review expertise, a combined workshop and training on GCP and Bioethics is organized in partnership with the existing GCP or Bioethics workshops sponsored by TDR, Bioethics network or other agencies. IVR provides support to potential investigators and institutions to participate in these workshops.

Role and Mission of the Initiative for Vaccine Research

The rationale for the establishment of the Initiative for Vaccine Research (IVR) in 2001 was to streamline the various vaccine research and development endeavours from different areas of WHO and from UNAIDS, organizing them so as to maximize synergies.

IVR's mandate is to provide a centralized source of leadership, vision, priority setting, and coordination with and/or of worldwide R&D efforts for the development of vaccines against neglected diseases, particularly in developing countries in which those diseases are endemic.

Within WHO, IVR is the key body responsible for drawing together the necessary expertise and efforts to address both worldwide priorities and gaps in capacity, as well as gaps in funding.

IVR works in close association with a wide range of WHO units, such as the UNDP/World Bank/WHO *Special Programme for Research and Training in Tropical Diseases* (TDR), the Communicable Diseases (CDS) cluster, the HIV/AIDS, Tuberculosis and Malaria (HTM) cluster and initiatives like Stop TB and Roll Back Malaria. It is also a counterpart within WHO for external partners and organizations like UNAIDS, the Global Alliance for Vaccines and Immunization (GAVI), the Program for Appropriate Technologies in Health (PATH), the International Vaccine Institute (IVI), as well as the many other public and private sector partners in vaccine R&D, whose contributions to the vaccine "pipeline" are vital.

Guidance and review of the work of the Initiative for Vaccine Research

The strategy, objectives and workplan of the Initiative for Vaccine Research are established following the recommendations of independent groups of international experts. The same groups have a mandate to review achievements against agreed milestones and to propose new avenues of research.

Expert external review: Steering Committees or Advisory Committees provide technical guidance on specific issues, whether on one particular disease, or a group of etiologically or symptomatologically linked diseases. These committees also review research proposals submitted to IVR for funding and usually meet annually.

List of Steering Committees/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 (TBVAC)

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)

Overall technical and operational review: 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 (STAC) and the Immunization, Vaccines & Biologicals Strategic Advisory Group of Experts (SAGE).

Financial notes

Total expenditure in 2002-2003 was USD 13 900 000

Of which 9 892 000 for activities

4 008 000 for salaries

Distribution of expenditure by disease areas