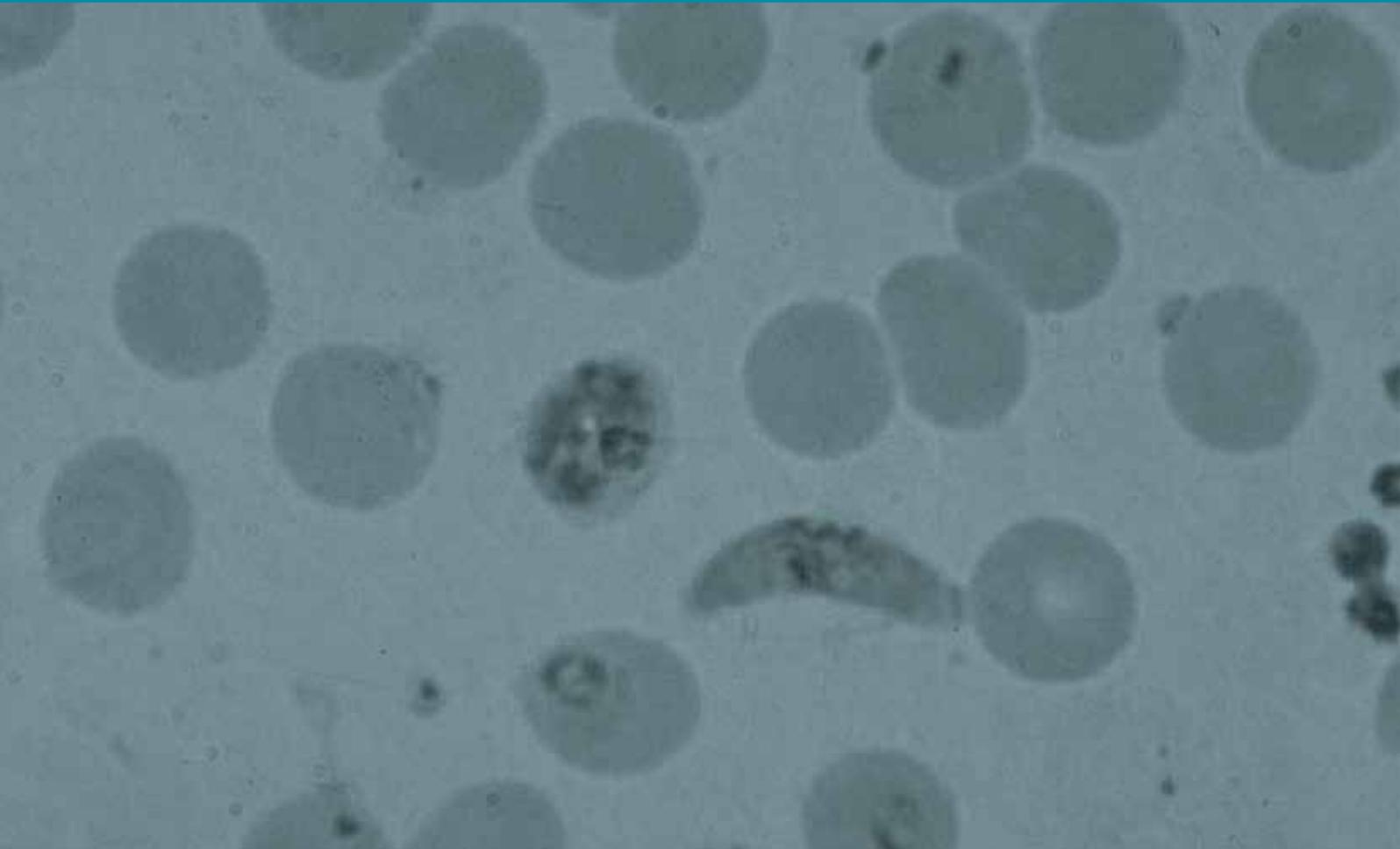


The Initiative for Vaccine Research **Report 2008–2009**

Department of Immunization,
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Abbreviations

AAVP	African AIDS Vaccine Programme
BCG	Bacillus Calmette-Guérin
CDC	Centers for Disease Control and Prevention
cGMP	current Good Manufacturing Practices
DCVMN	Developing Country Vaccine Manufacturers' Network
DNA	deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
EPI	Expanded Programme on Immunization
EVI	European Vaccine Initiative
GAP	Global Action Plan to Increase the Supply of Influenza Vaccines
GHAVE	Global HIV Vaccine Enterprise
GLP	Good Laboratory Practice
Hib	<i>Haemophilus influenzae</i> type b
HPV	human papillomavirus
IAVI	International AIDS Vaccine Initiative
IND	investigational new drug
IPR	intellectual property rights
IVAC	IVR Vaccine Advisory Committee
LAIV	live attenuated influenza vaccines
MDG	United Nations Millennium Development Goal
MVI	Malaria Vaccine Initiative
MVP	Meningitis Vaccine Project
NA	neuraminidase
NIH	United States National Institutes of Health
NRA	national regulatory authority
NVI	Netherlands Vaccine Institute
PCR	polymerase chain reaction

PCV	pneumococcal conjugate vaccines
PRNT	Plaque reduction neutralization test
QUIVER	Advisory Committee on Quantitative Research in Immunization
SAGE	WHO Strategic Advisory Group of Experts on immunization
TB	tuberculosis
TRIPS	Agreement on Trade Related Aspects of Intellectual Property Rights
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNFPA	United Nations Population Fund
WIPO	World Intellectual Property Organization

1 Introduction

The Initiative for Vaccine Research (IVR) brings together under one umbrella the multiple vaccine and related implementation research activities of the World Health Organization (WHO). Its mission is to accelerate the development and optimal use of new and improved vaccines and technologies, with a special focus on developing country needs. At the end of 2009, IVR had been carrying out this mission for 10 years, and had a core staff of 25, seconded by consultants and other external support as required. This report describes progress towards the objectives of the Initiative during 2008–2009.

As highlighted in the State of the world's vaccines and immunization,¹ the first decade of this century was the most productive in the history of vaccine development. Not only have the traditional paediatric vaccines been improved, and their use increased, but many new vaccines are now available and even more are in the pipeline. Available vaccines against pneumococcal and diarrhoeal diseases can now start to reduce the huge toll of death and disability they cause in developing countries. Within the next few years, new vaccines may also have an impact in poor countries on cervical cancer, meningitis and, with sustained efforts, even malaria and other diseases that disproportionately affect the poorer populations of our planet. An aerosolized measles vaccine, due to be available within the next biennium, should significantly facilitate the reduction, and eventual elimination of this disease worldwide.

However, the last biennium was also marked by a number of unexpected, yet very real threats to health across the globe. For vaccine-preventable diseases, as in other areas, this placed heavy demands on government health services and the vaccine research and development (R&D) community. Perhaps the most remembered of these threats may be the A(H1N1) influenza pandemic in 2009, which generated unprecedented collaboration among WHO, Member States and the vaccine industry to defy deadlines to mitigate the threat.

Another challenge to vaccine R&D over 2008–2009 was an economic recession that particularly hit health and social sectors that were already fragile. WHO was not immune to the impact of precarious financing and took steps to put this issue on the agenda at the highest level. Research into vaccines against three diseases – HIV, malaria and tuberculosis – had made significant headway although investment would need to be intensified to reduce the four million people who die each year from this trio, mostly in developing countries.

IVR took these challenges on board in the implementation of its workplan and was highly successful in meeting – and even surpassing – the expected results it had set at the beginning of 2008. The following are highlights of these achievements.

Guarded optimism for an HIV vaccine: The first positive results of protection against HIV infection were reported in September 2009 from a large test-of-concept trial in

Thailand. Although these are early days, the results have instilled new hope among HIV vaccine researchers that a safe, effective vaccine against the pandemic may one day be on the market.

HIV gets a new voice for Africa: After 10 years of operating under the wings of IVR, the African AIDS Vaccine Programme (AAVP) is becoming a fully-fledged African organization based at the Uganda Virus Research Institute in Entebbe. Building on the success of the AAVP, plans for a similar network in Asia have been initiated.

Capacity strengthening for developing country influenza vaccine manufacturers doubled: At the end of December 2009, 11 developing country vaccine manufacturers were receiving seed grants and technical assistance to acquire the capacity to produce influenza vaccines, compared to 6 in 2007. Four grantees initiated clinical trials with an H1N1 vaccine and another had a seasonal influenza vaccine licensed. The International Technology Transfer Platform based in the Netherlands provided training and technology transfer for the emerging producers. In addition, IVR secured a royalty-free licence with the owner of a live attenuated influenza vaccine technology, enabling virus seed strains to be transferred under sub-licence to two grantees as well as a Chinese manufacturer.

Meningitis vaccine within reach: The good safety and immunogenicity results from clinical trials of a meningitis A conjugate vaccine led to market authorization in India in December 2009, paving the way for WHO prequalification of the vaccine. The GAVI Alliance is already committed to help introduce the vaccine in three countries in the African Meningitis Belt during 2010–2011.

Five new policy papers issued: As the research arm of the WHO Strategic Advisory Group of Experts on immunization (SAGE), IVR conducts detailed technical analyses and appraises the suitability of methods to inform the immunization policies recommended by SAGE. During the reporting period, five position papers were issued based on technical background prepared by IVR on the use of vaccines against cholera, cervical cancer, typhoid, H5N1 influenza virus in the inter-pandemic period, and rotavirus vaccines at global level.

Moving ahead with malaria vaccines: As the most advanced malaria vaccine candidate reached the pivotal phase III stage in May 2009, IVR and the Global Malaria Programme established a Joint Technical Expert Group to advise on the data needed for eventual WHO policy recommendations. IVR also led the technical agenda for a multi-agency meeting which agreed on the standardization and strengthening of the clinical challenge model in malaria. This will have a central role in the development of malaria vaccines.

While optimism about the malaria situation must be cautious, this is the first time, in decades, that we are getting some good news. This, too, is progress.

WHO Director-General to the Executive Board, 18 January 2010

Guidelines for vaccine R&D: A major focus of IVR's mandate is analysing the evidence to set norms, standards and policies for research related to vaccine development and introduction. During 2008–2009, guidelines were published on the evaluation of dengue vaccines in endemic areas, which proved seminal in the design of a large-scale proof-of-concept clinical trial being conducted in Thailand. Other guidelines included the standardization of economic evaluations of immunization programmes, in response to the need for transparency, completeness and comparability of data.

IVR IN THE COMING DECADE

A new decade provides opportunities to take stock of vaccination research needs, and the capacity of stakeholders to meet these needs. In 2009, following an extensive consultation process, WHO launched its new strategy on research for health, complemented by the Global plan of action on public health, innovation and intellectual property. IVR, as the research component of the WHO Department of Immunization, Vaccines and Biologicals, contributed to shaping these policy documents and aligned its Strategic Plan 2010–2020² with the major underlying principles, namely: helping to define priorities, supporting standards and guidelines, strengthening country capacity, and ensuring the effective translation of research findings into policy and practice, particularly for diseases afflicting developing countries.

Innovation is increasingly used to enable access of developing countries to technologies otherwise out of their reach. Of particular note has been the successful sublicensing of technology to IVR grantees to produce influenza vaccine, and the Global Adjuvant Vaccine Initiative whereby developing country manufacturers can develop vaccines using adjuvants free of intellectual property barriers.

IVR also remains committed to the goals of the Global Immunization and Vaccine Strategy, particularly its Strategy 10 to promote research and development of vaccines against diseases of public health importance.

Ten years into its mandate, IVR's vision and mission remain unchanged. What will change is the need to work even more within partnerships to reach common goals. IVR is proud of its achievements over the last biennium, and looks forward to accelerating action to improve health through vaccine research in the future.

2

Knowledge and partnerships

2.1 Reviewing the latest scientific advances

2.1.1 Global Vaccine Research Forum

The Global Vaccine Research Forum brings together every 18 months around 200 experts and interested parties in the field of vaccine and vaccination R&D. The eighth and ninth meetings of the Forum were convened by IVR in June–July 2008 and December 2009, respectively.

At the eighth Forum and satellite symposia, two keynote addresses reflected on the likelihood of an HIV vaccine becoming a reality, and on successes and failures with different types of malaria candidate vaccines. In addition to updates on a number of diseases and vaccines, issues of growing interest included how to improve access to immunization, and the public health value of therapeutic vaccines to fight chronic viral infections and noncommunicable diseases. The GAVI Alliance presented an outline of its new strategy 2009–2013 and a short-list of priority diseases and vaccines, developed with input from IVR. Finally, satellite symposia focused on the use of vaccine and vaccination cost–effectiveness models, and on increasing immunity in older population groups.

Six sessions and complementary satellite symposia were held during the ninth Global Forum in 2009. Discussion on the *status of vaccines against malaria* focused principally on vaccine efficacy analyses, clinical and regulatory challenges, and the impact of vaccines on transmission, particularly in Africa. H1N1 pandemic vaccine development issues took centre stage during the session on *seasonal and pandemic influenza vaccine R&D*. Presentations were also made on the status of the IVR programme to build influenza vaccine production capacity in developing countries, prospects for a universal seasonal influenza vaccine, the burden of infectious respiratory diseases in Africa, as well as an ongoing influenza vaccination trial in Senegal.

Regarding *GAVI priority diseases*, updates were presented on the forthcoming licensing of MenAfriVac®, the need for effective surveillance to evaluate the impact of pneumococcal conjugate vaccine use, and lessons learnt from Hib vaccine introduction in Mali. The session on *pharmacovigilance in low- and middle-income countries* noted the advances of the Brighton Collaboration to establish standards based on the highest quality scientific evidence for adverse events following immunization. Two specific projects were described: INYVAX, and the Global Vaccine Safety Blueprint, a WHO project to enhance vaccine safety monitoring, investigation and response. More efforts were still needed to collect data from developing countries.

How to *optimize vaccine supply and logistic systems* to cater for the introduction of many new vaccines in the coming years was considered a critical and underestimated issue. Projects addressing the challenges of increased volumes of vaccines with diverging temperature requirements were those conducted by the

WHO Vaccine Presentation and Packaging Advisory Group, and Project Optimize. Good progress had been made in global *measles control* as all WHO regions, with the exception of South-East Asia, had achieved the goal of reducing measles mortality by 90% compared to 2000 levels. Challenges include weak immunization systems, reduced financial and political commitment (in part due to recent successes), and incomplete implementation of strategies. Operational and research priorities were presented, along with challenges for eradication of the disease, the measles aerosol project, measles DNA vaccine priming for infants, and rubella control and elimination strategies in the Americas.

The highlights of the satellite symposia on correlates of protection, new vaccine platforms and herd effects in vaccine effectiveness were presented in a plenary session, along with preliminary data from the Global Enteric Multi-centre Study on the etiology of diarrhoeal and enteric diseases in sub-Saharan Africa and Asia.

Reports of meetings of the Global Vaccine Research Forum are posted on the IVR web site at www.who.int/vaccine_research/links/GIVaReFoRe/en/index.html.

2.1.2 HIV vaccine efficacy trial results

The continued spread of the HIV pandemic underlines the need for more research into novel HIV prevention tools such as vaccines. At the same time, HIV vaccine R&D is facing some difficult hurdles, one of which is the lack of knowledge on correlates of protection against infection or the development of disease. This has led to the parallel development and testing of vaccination strategies in different parts of the world. One of the few vaccine candidates to have reached an advanced stage of development is a recombinant rgp120 vaccine tested in two phase III efficacy trials in men-who-have-sex-with-men in the USA, and in a cohort of injecting drug users in Thailand. Both trials showed the vaccine to be safe, but did not show a significant level of protection against HIV infection. Another promising candidate vaccine based on *Adeno5* was tested in two trials known as STEP (in Australia, Canada and the USA) and Phambili (in South Africa). However, these trials had to be discontinued due to a potentially enhanced risk of HIV infection in vaccinated individuals who were not circumcised and had high levels of pre-existing immunity to the vaccine *Adeno5* vector.

The first positive results of protection against HIV infection were reported in September 2009 from a large test-of-concept trial in 16 395 adult volunteers in Thailand. The evaluation of a novel HIV vaccine regimen with two different candidate vaccines revealed a statistically significant level of protection against HIV infection in 31.2% of vaccinated volunteers by the modified intention-to-treat method. The same level of protection could not be reached using two other methods, despite visible trends in favour of protection. At the same time, this vaccine regimen had no impact on the control of the viral load in vaccinated individuals who became infected. No vaccine safety issues were observed in the trial.

The results have instilled new hope that a safe and effective HIV vaccine may one day become available. However, the WHO-UNAIDS HIV Vaccine Advisory Committee, which characterized the results as modestly protective, cautioned that more work was needed to understand potential mechanisms of protection and duration. Most importantly, it remained to be seen if the two vaccine components in this particular regimen would be effective in other parts of the world with diverse host genetic backgrounds and different HIV subtypes.

WHO and UNAIDS have been involved in this trial since 1991.³ During 2008–2009, a joint Coordinating Group was established to assist the principal investigators to prepare for the release of the Thai trial results and their interpretation by national health authorities and the public.

2.1.3 Pandemic influenza vaccines

INFLUENZA VACCINES THAT INDUCE BROAD SPECTRUM AND LONG-LASTING IMMUNE RESPONSES

On 9–10 November 2009, IVR and the Wellcome Trust convened the fourth meeting on influenza vaccines that induce broad spectrum and long-lasting immune responses.⁴ Participants reviewed the status of research, including on influenza vaccines that could provide cross-protection against viruses from the same or different subtypes. A series of presentations focused on known and exploratory mechanisms of humoral and cellular immune protection against influenza virus infection. Results obtained in different settings have shown that school-based vaccination with live attenuated influenza vaccines (LAIV) induced significant reduction in overall acute respiratory illness rates in intervention areas among different age groups, suggesting that lower circulation of influenza virus among vaccinated children reduces the exposure of older persons. New candidate LAIVs under development induce protection in animal models against homologous and antigenically distinct heterologous influenza virus challenge infection, and further studies in the area were encouraged (see also Section 2.2.3).

Considerable progress was noted in the development and evaluation of adjuvanted influenza vaccines. Previous experience with AS03-adjuvanted egg-derived, split virion H5N1 vaccine facilitated rapid pandemic A(H1N1) vaccine development and registration in 2009. MF59-adjuvanted influenza vaccines, formulated as monovalent H5N1 or tetravalent seasonal vaccine with added H5N1 valency were used in various prime-boost schedules. No differences were observed in serologic responses, regardless of the vaccine combination.

Data were presented on several new technologies for influenza vaccines, such as virus-like particle-based vaccines, live viral vectors and M2e-based vaccines. Little is known on the potential protective efficacy of most of these in humans, and much more has to be learnt on their immunogenicity and principal characteristics. Notwithstanding, they may pave the way to a universal influenza vaccine.

EVALUATION OF PANDEMIC INFLUENZA PROTOTYPE VACCINES IN CLINICAL TRIALS

The 4th and 5th meetings on the evaluation of pandemic influenza prototype vaccines in clinical trials were held on 14–15 February 2008 and 12–13 February 2009, respectively. Both reviewed the latest data on the immunogenicity, safety, dose response and possible antigen-sparing, as well as cross-reactivity of the antibody response elicited by H5N1 prototype vaccines. All preparations evaluated in clinical trials were shown to be safe and well tolerated in healthy adult volunteers and, when tested, in children and the elderly. It was noted that comparison of different vaccines or adjuvants was difficult in the absence of properly standardized antibody assays, and that standard operating procedures for haemagglutination inhibition and neutralizing antibody assays, as well as international reference reagents, were urgently needed.

Substantial progress had been achieved in the assessment and characterization of prototype pandemic vaccines, particularly with respect to immunogenicity in children and the responses elicited by prime-boost strategies. Among the H5N1 vaccines evaluated, the egg derived split/subunit, oil-in-water adjuvanted vaccines had demonstrated dramatic antigen sparing, cross-clade immune responses, and effective priming. Because oil-in-water preparations had induced higher homologous and broader heterologous antibody responses than their non-adjuvanted counterparts, studies are underway to apply this adjuvant technology to seasonal influenza vaccination among elderly at-risk groups. More data should be accumulated in groups that would be among first targets in the event of an influenza pandemic, especially in the 6 months–3 years age group.

More studies were also considered necessary to predict better the protective efficacy of prototype pandemic vaccines, especially those using novel technologies and live attenuated vaccines. Recent studies had shown the potential for two-dose priming regimens to elicit long-term immunologic memory associated with rapid and, in the case of adjuvanted vaccines, broadened antibody responses following heterologous boosting. Data from other studies in progress were presented and research requirements noted, such as how virus-specific CD4+ T cells and memory B cells in H5N1 vaccinated individuals correlated with protection. Studies in ferrets and perhaps non-human primates may be a priority along with human challenge studies, although considerable funds would be required.

DATABASE OF CLINICAL TRIALS ON CANDIDATE PANDEMIC INFLUENZA VACCINES

In order to share the latest data on prototype pandemic influenza vaccines with the widest possible audience, IVR continued to maintain its Internet database of non-restricted information on clinical trials of candidate influenza vaccines.⁵ This is regularly updated with data presented at scientific and technical meetings and

complemented with data from publications and direct contacts with manufacturers and investigators. In addition to prototype pandemic influenza vaccines against H5 haemagglutinin subtype influenza A viruses, most producers became involved in 2009 in clinical trials of candidate pandemic influenza A(H1N1) vaccines, the results of which will be included in the next update of the database in 2010.

The spreadsheet presentation of the data allows users to filter according to 12 variables, e.g. type of vaccine, virus strain, adjuvant used, age, schedule and route of administration. The time frame of the trials, along with hyperlinked references and comments, are also provided. In August 2009, more than 70 clinical trials were ongoing or completed. While most of the trials focus on healthy adults, new data are now available on the safety and immunogenicity of vaccines in the elderly and in children. IVR encourages all those involved in influenza vaccine trials to share information on planned and ongoing activities for inclusion in the database.

THE ROLE OF NEURAMINIDASE IN INDUCING PROTECTIVE IMMUNITY AGAINST INFLUENZA INFECTION

The USA/WHO-organized meeting on correlates of immune protection against influenza in December 2007 recommended further studies on comparison and standardization of assays to evaluate anti-NA immune responses. Since then, research related to neuraminidase (NA) has advanced considerably. Results of some animal model studies raise the hypothesis that certain individuals have a degree of resistance to H5N1 infection induced through exposure to seasonal influenza virus or vaccine. To revisit the topic in light of the new data, IVR convened a satellite meeting on the role of NA in inducing protective immunity against influenza infection during the European Influenza Conference held in Vilamoura, Portugal. Participants reviewed the status of research; discussed new approaches for simpler and more reproducible assays to detect anti-NA immunity and to quantify NA in vaccines; and proposed as a priority activity the standardization of immunological assays.⁶

2.1.4 Malaria phase III clinical trial initiation

May 2009 was a landmark date with initiation of the randomized placebo-controlled phase III trial of RTS,S/AS01, the most advanced malaria *P. falciparum* vaccine candidate. The trial involves 11 sites in 7 countries in sub-Saharan Africa (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and the United Republic of Tanzania). As of December 2009, over 6500 children had been enrolled in the trial. The completion of enrolment of a total of 12 000–16 000 children is estimated at the fourth quarter of 2010 with two age groups, 5–17 months at first immunization and 6 weeks at first immunization. The younger group will receive malaria vaccine co-administered with routine EPI vaccines. GlaxoSmithKline and the PATH Malaria Vaccine Initiative are joint developers with funding by the Bill & Melinda Gates

Foundation. RTS,S/AS01 had shown 51% efficacy against clinical malaria over 17 months in a phase II trial in Kenya and the United Republic of Tanzania. Paediatric efficacy has also been demonstrated in several other trials in Mozambique. The vaccine development partnership incorporated guidance provided by the IVR Malaria Vaccine Advisory Committee for phase III trial design, analysis methods, choice of case definitions and efficacy endpoints.

2.1.5 Rotavirus safety and efficacy trials

Rotaviruses are the most common cause of severe diarrhoeal disease in young children throughout the world. Two oral, live, attenuated rotavirus vaccines are available internationally, both of which are considered safe and effective in preventing gastrointestinal disease caused by rotaviruses. However, until effectiveness and safety had been confirmed in all regions, and since other live attenuated oral vaccines had been shown to be less effective in poor sanitary conditions, WHO could not recommend rotavirus vaccines for inclusion in all national immunization programmes.

Trials of the two rotavirus vaccines were thus conducted in Asian and African countries with high mortality from diarrhoeal diseases, different child mortality strata, and where sanitation is poor. In 2009, the Strategic Advisory Group of Experts (SAGE) reviewed new information on the immunogenicity and efficacy of the vaccines from these trials, as well as post-licensure monitoring data. After a year of follow-up, the efficacy of one vaccine in preventing severe rotavirus gastroenteritis was 61.2% in the combined study populations in Malawi and South Africa. In clinical trials in Asian countries with low or intermediate mortality rates for children aged <5 years, this vaccine had a combined efficacy of 96.1% in protecting against severe rotavirus gastroenteritis. IVR cosponsored the early phases of some of these studies in partnership with PATH and played an active role in the design of the trials.

The phase III trial of the second vaccine showed the efficacy of a 3-dose regimen against severe rotavirus gastroenteritis after a year of follow-up to be 64.2% in Africa and 51.0% in Asia. IVR had been involved in the selection of sites and the study design.

In December 2008, the WHO Global Advisory Committee on Vaccine Safety reviewed the safety data from phase III efficacy studies of these vaccines, as well as postmarketing safety data from Australia, Latin America and the USA. The Committee concluded that the vaccines were safe and that a risk of intussusception of the order associated with the now withdrawn tetravalent reassortant rotavirus vaccine could be ruled out with confidence. Taking into account the new evidence, WHO now recommends that infants worldwide be vaccinated against rotavirus (see also Section 4.1).

2.2 Increasing innovation and access to vaccines in developing countries

2.2.1 Global Adjuvant Development Initiative

The development of vaccines, particularly in the public sector, is severely hampered by the lack of access to appropriate adjuvants, and to expertise in vaccine formulation. Many vaccine candidates are abandoned during late preclinical or early clinical development due to formulation or reactogenicity issues that could have been addressed with access to reagents and know-how. Following much groundwork, two centres are now collaborating with IVR to develop and supply adjuvants, and provide expertise in vaccine formulation. The objective of the centres – the Infectious Disease Research Institute (IDRI) in Seattle, USA, and the Department of Biochemistry in Lausanne, Switzerland – is to facilitate the development of new vaccines in the public sector where access to adjuvants and know-how on vaccine formulation is limited. IVR provides technical support to the centres, and aids in the dissemination of their products and services.

The laboratory in Seattle has provided to vaccine developers a wide range of adjuvants, including GLA, a novel synthetic TLR-4 agonist similar in its mode of action to the adjuvant used in one proprietary malaria vaccine candidate; and stable squalene-based emulsions, similar to the squalene-based adjuvants used in H1N1 influenza vaccines. Following agreement on terms and conditions with IDRI, vaccine researchers worldwide developing HIV, malaria and tuberculosis vaccines are using these adjuvants and the know-how supplied, free of intellectual property barriers, to develop vaccine formulations that achieve high levels of immunity.

Under contract with IVR, this centre also carried out an evaluation of adjuvants for dose-reduction of the injectable polio vaccine (IPV), and demonstrated that simple non-proprietary oil-in-water emulsions can permit at least a 10-fold reduction in dose. Transfer of the adjuvant production process technology was therefore initiated for production and clinical evaluation of the low-dose IPV vaccine in India.

The centre in Lausanne (a WHO Collaborating Centre on immunology research and training) is developing knowledge on vaccine formulation and characterization. Plans are underway to expand training on this topic to developing country vaccine manufacturers.

In 2009, when supplies of H1N1 influenza vaccine were limited, adjuvants were scrutinized for their potential to permit dose-reduction and thus increase the capacity of available vaccine. IVR facilitated the evaluation of safety and benefit of such vaccines at numerous meetings, such as the virtual consultation on the safety of adjuvanted influenza vaccines held on 3 June 2009.⁷

2.2.2 Technology transfer for influenza vaccine production

In 2008–2009, the IVR programme to enhance the capacity of developing country manufacturers to produce seasonal or pandemic influenza vaccine was further expanded. In line with the objectives of the Global Action Plan to Increase Influenza Vaccine Supply,⁸ two avenues for this capacity strengthening were pursued: grant awards and the establishment of a technology transfer platform.

A. Grant award scheme

Thanks to international stakeholder support to the project, * five new grants were awarded to vaccine manufacturers, bringing the total number of grantees to date to 11. The status of progress on all grants as at December 2009 is summarized below.

COUNTRY/ INSTITUTE	TECHNOLOGY/MAIN ACHIEVEMENTS
Brazil/Instituto Butantan (Year 2)	Egg-based inactivated split and/or whole virion H5N1 with adjuvant. Now owns seasonal production technology. Ten experimental lots of novel or pandemic vaccine produced in new pilot plant (H3N2, H5N1, H1N1). Clinical trial of experimental H5N1 and H1N1 vaccines is imminent.
Egypt/Vacsera (Year 1)	Small-scale facility to produce egg-derived whole virion influenza vaccine. Activities in 2009 focused on the conceptual design and Site Master Plan. The company concluded a collaborative agreement for technology transfer with Netherlands Vaccine Institute (NVI) for the lifetime of the project, i.e. beyond the scope of the present grant.
India/Serum Institute of India (Year 2)	Egg-based technologies: whole virion alum adjuvanted inactivated influenza vaccine; and LAIV using WHO-sublicensed Russian technology. Pandemic H1N1 LAIV has entered clinical trial. Inactivated pandemic H1N1 candidate vaccine produced and clinical evaluation is planned in January 2010.
Indonesia/Bio Farma (Year 2)	Fill-finish facility and upstream vaccine antigen production unit with Japanese technology for seasonal split egg-based product. Facility established and a seasonal trivalent vaccine developed and approved by the National Regulatory Authority (NRA) for the domestic market. Currently establishing a new antigen production unit using technology transfer. Pandemic H1N1 lots were produced for clinical trial in 2010.
Islamic Republic of Iran/Razi Institute (Year 1)	The Institute, an established producer of paediatric vaccines, intends to develop an egg-based influenza vaccine in a small-scale plant. The grant covers equipment and staff training. Autoclaves for production areas were purchased and technology transfer is under negotiation with NVI.
Mexico/Birmex (Year 2)	Egg-based split vaccine in a blending, filling and packaging facility. All project goals reached: product-specific equipment for quality control laboratory purchased and construction and engineering plans for blending facility completed.

* particularly the US Department of Health and Human Services, the Government of Japan through UNICEF, the Asian Development Bank and the Governments of Canada and the United Kingdom.

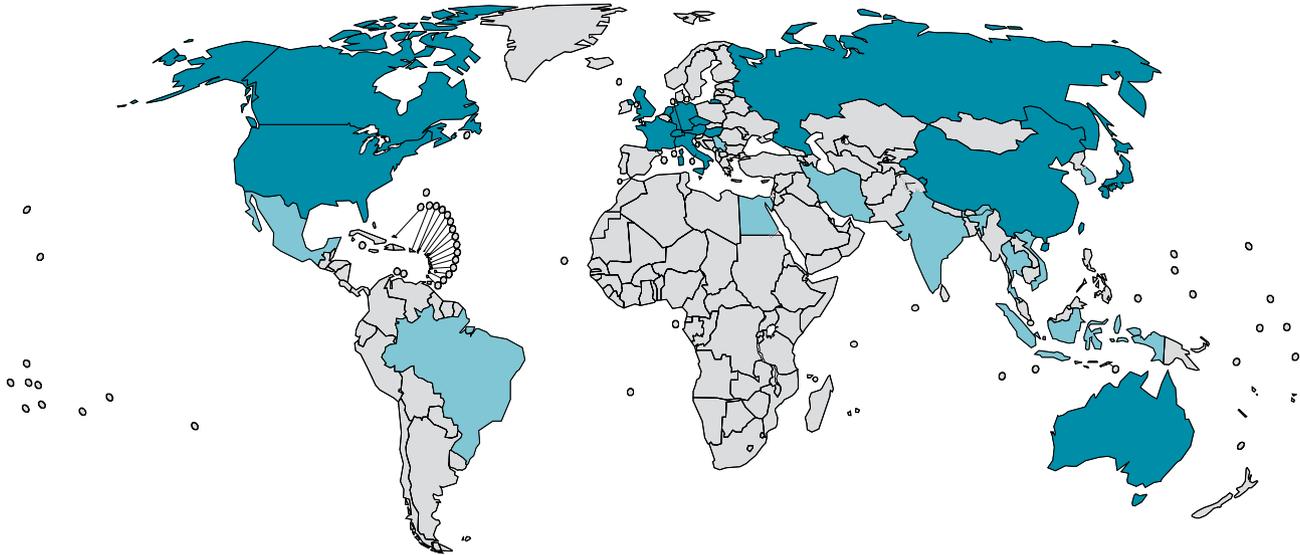
Republic of Korea/ Green Cross Corporation (Year 1)	A large, recently licensed producer of egg-based split seasonal vaccine. The grant is to establish a dedicated pilot plant facility for H5N1 influenza vaccine production. For clinical evaluation, an alum adjuvanted whole virion H5N1 lot was produced. Split (A)H1N1 (non-adjuvanted) pandemic vaccine was evaluated in a phase I/II clinical trial and approved by the NRA.
Romania/ Cantacuzino Institute (Year 1)	A small-scale producer of seasonal egg-based inactivated split influenza vaccine. The project includes production optimization, and preclinical and clinical studies. Pandemic (A)H1N1 lots were produced, a clinical trial in adults completed and the vaccine approved by the NRA for adult immunization in Romania.
Serbia/Torlak (Year 1)	Torlak plans to build a new filling department. A tender for main equipment was organized in line with local regulations and offers from potential basic design contractors received.
Thailand/ Government Pharmaceutical Organization (Year 2)	Egg-based technologies: split inactivated seasonal vaccine and LAIV using WHO sublicensed Russian technology for pandemic surge capacity. A renovated pilot plant compliant with cGMP was approved by the NRA for clinical trial lot production. Clinical trials with pandemic (A)H1N1 LAIV were initiated in December 2009. Processes were also established for production of seasonal split inactivated vaccines.
Viet Nam/IVAC (Year 2)	Small-scale production facility for egg-derived whole virion, alum adjuvanted influenza vaccines and construction of a small chicken farm for egg supply. The newly built plant reached the final stage of validation end 2009, and a collaborative agreement for technology transfer was established with NVI.

Influenza activities took on a new urgency with an outbreak in humans of an H1N1 influenza strain from swine origin, culminating in the WHO declaration of the first influenza pandemic of the century in June 2009. This had an immediate effect on the programme of many grantees, as the most advanced switched their focus from H5N1 to the new pandemic strain. The H1N1 pandemic served as an opportunity to test the robustness of the IVR programme. Experience gained by the grantee manufacturers to date proved successful, as they produced more than six H1N1 lots, some of which were already in clinical trials as at December 2009. In addition, two pandemic vaccines were licensed for pandemic use by the National Control Authorities, and more lots are expected to be produced for clinical trials during the first quarter of 2010.

Since its inception, the IVR project has seen more than US\$ 40 million invested in seed grants, technology transfer, training and support to the technology platform and LAIV activities. IVR financial and technical assistance, along with intensive monitoring, and oversight from the Technical Advisory Group, has significantly broadened

the number of developing countries able to produce influenza vaccine. However, geographical imbalances still exist in eastern and central Asia and sub-Saharan Africa, as illustrated in Figure 1.

FIGURE 1. INFLUENZA VACCINE PRODUCERS IN 2006



- Countries with influenza vaccine production capacity in 2006
- Countries with new or planned influenza vaccine production capacity after 2006

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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B. International Technology Platform for Influenza Vaccine

To overcome the lack of available influenza technology providers, IVR established a technology hub to provide developing country manufacturers with a package of training and materials for influenza production. The Netherlands Vaccine Institute (NVI), a recognized training centre for developing country manufacturers, became fully operational in 2008 as a state-of-the-art international technology platform for influenza vaccine. The NVI has established an egg-based seasonal influenza

vaccine production process suitable for scaling up, training and technology transfer to vaccine manufacturers meeting WHO quality/viability criteria in low- and middle-income countries. The pilot-scale process uses semi-automated equipment to produce inactivated whole virus vaccine, although subunit, split or tissue culture vaccines are considered for the future. The process can also be applied to potential pandemic vaccines.

Progress also included the development of clinical protocols as a first step towards clinical trials. Hands-on training courses, including the production of a vaccine lot, were provided to IVR grantee personnel. Finally, bilateral collaboration enabled the initiation of transfer of an influenza technology package free of intellectual property to two developing countries grantees, namely Vacsera in Egypt and IVAC in Viet Nam.

2.2.3 Live attenuated influenza vaccine

The development of live attenuated influenza vaccines (LAIV) became a priority of the Global Action Plan to Increase Influenza Vaccine Supply because of their inherent high production yield (see also Section 2.1.3). In order to facilitate pandemic surge capacity in developing countries, IVR secured a royalty-free licence on the Russian LAIV with the owners of the technology. The non-exclusive licence for egg-based vaccines allows IVR to provide developing country manufacturers with virus seed strains from the Institute of Experimental Medicine (IEM), the original developer of a LAIV vaccine in Russia. In 2009, three such sublicences were successfully concluded with developing country vaccine manufacturers in China, India and Thailand. Two of these, the Government Pharmacological Organization in Thailand and the Serum Institute of India, initiated clinical trials with a LAIV pandemic A(H1N1) product in December 2009.

During the biennium, IVR also supported an upgrade of the IEM influenza facilities. Additional funds were allocated to the safety and efficacy evaluation of pandemic A(H1N1) LAIV vaccines in ferrets and other animal models. The vaccines, produced by the Russian licensed manufacturer of the product, were derived from seed strains distributed by IEM.

2.2.4 Intellectual property rights issues

With a view to increasing an understanding of the role and impact of intellectual property rights (IPR) on vaccine development, production and access, a workshop was co-organized in Tokyo, Japan in November 2009 by IVR and the Developing Country Vaccine Manufacturers' Network (DCVMN). Around 20 developing country manufacturers from the public and private sectors were briefed on a broad range of issues related to IPR and prerequisites for an effective vaccine innovation system.

With regard to IPR relevant to vaccine R&D and production, and the implications of the TRIPS Agreement, it was noted that developing countries may expect barriers

in accessing vaccine products and technologies as interest in new vaccines increases. Strengthening the capacity of developing countries to consider the legal and technical options related to IPR management is therefore needed. Innovative approaches that are equitable for both the licensor and potential licensee should also be explored, such as patent pooling and open licences, which can promote access to technology and know-how on vaccines in developing countries.

An examination of the resources needed to obtain relevant patent information showed significant obstacles for developing countries, notwithstanding the databases of WIPO and others. In this respect, patent landscaping such as the WHO-WIPO-PIIPA* study on the H5N1 influenza virus can be used as a preliminary insight into potential blockages in different territories. An analysis of the scope of patent claims and freedom-to-operate will also determine potential barriers to production. A third option to overcome barriers to generic production was discussed, i.e. the use of patent oppositions and challenges, as the proportion of invalid patents is high, particularly for genetic sequences and biological resources. These analyses were considered pivotal for the decision-making process of vaccine manufacturers.

An effective way to facilitate access to know-how on vaccine production in the developing world has proven to be the transfer of technology. Participants explored various economic contexts and potential models for technology transfer, particularly technology platforms such as the Netherlands Vaccine Institute which is facilitating local influenza vaccine production in developing countries.

Participants concluded that a continuing forum and training courses, e.g. on-line modules targeting their specific needs on IPR and licensing issues, would be very welcome. In addition, a web site and/or database were recommended for DCVMN members to be able to access data from patent searches and landscaping studies in a user-friendly format. The DCVMN would explore activities to improve the capacity of developing country vaccine manufacturers to address IPR, innovation and vaccine production issues.

2.3 Prioritizing research needs

2.3.1 Malaria vaccine candidates

Several lines of evidence, including a partially effective first generation malaria vaccine, support the feasibility of developing a more efficacious second generation malaria vaccine in the longer term. However, the design of candidate malaria vaccines remains empiric because much of the knowledge needed to rationally design vaccines and predict clinical efficacy is not available. Access to assay or

* PIIPA (Public Interest Intellectual Property Advisors, Inc.) is an international non-profit organization that avails intellectual property counsel to developing countries and public interest organizations who seek to promote health, agriculture, biodiversity, science, culture and the environment.

challenge trial results which correlate with paediatric field efficacy can potentially accelerate timelines considerably. IVR is facilitating work on the following factors within the global malaria vaccine community which can all reduce empiricism over time: comparative evaluation, assay and model standardization (see 4.2), greater information sharing, collaboration and coordination between groups, and rigorous evaluation of existing datasets. This work is partly carried out with the Malaria Vaccine Funders Group, and partly by engaging directly with the R&D community.

The sporozoite challenge trial is now generally accepted as a determining criterion for the development pathway for pre-erythrocytic malaria vaccines. A harmonized, consensus-based clinical challenge protocol will have a major part to play in rational decision-making on malaria vaccine prioritization. With this in mind, in March 2009, IVR led the technical agenda development for a WHO, PATH-MVI, EVI and USAID joint meeting on optimizing the use of the clinical challenge model for evaluation of candidate blood stage malaria vaccines.⁹ Follow-up on recommendations of this meeting include harmonization of microscopy standard operating procedures for clinical challenge trials and identification of a reference centre for quantitative PCR assays. In 2010–2011, IVR aims to generate a consensus-based document on the core set of challenge trial procedures to be harmonized among centres globally.

During 2009, the IVR tables of preclinical and clinical malaria vaccine development projects were updated to include more information in a spreadsheet format.¹⁰

2.3.2 Vaccination strategies for all age groups

Changing epidemiological patterns and new vaccines have made possible a reappraisal of the boundaries of traditional paediatric immunization. Vaccination beyond infancy is a major goal of the Global Immunization Vision and Strategy 2006–2015 and, in 2009, became a priority project for IVR. Adolescents and the elderly are two age groups receiving particular attention.

Recently, the new human papillomavirus (HPV) vaccine opened the door to exploring vaccination in adolescent girls along with other interventions. In 2009, IVR carried out a review of immunization in this population group¹¹ and co-published an article on experiences with adolescent immunization in low- and middle-income countries.¹² IVR works closely with other WHO programmes in this area, particularly those involved in cancer control and in reproductive health.

The elderly suffer significant illness from infectious diseases, yet existing vaccines may have limited effectiveness in this population group, who are doubly vulnerable to respiratory and opportunistic infections as the immune system weakens with age. To date, very few studies have documented the infectious disease burden in this

group, and no studies have ever measured the immune function in the elderly in developing country populations, where frequent exposure to infectious agents may lead to different onset patterns. In 2009, a project was presented to the IVR Vaccine Advisory Committee (IVAC) summarizing the considerable gaps in knowledge in this population group and providing a step-wise plan to develop a research agenda that could ultimately lead to an immunization policy for healthy ageing. IVAC considered this to be a useful and innovative research topic and that IVR was in a good position to coordinate a long-term strategy with its partners, starting with the gathering of data to document the situation.

2.3.3 Optimizing immunization schedules

The current EPI vaccine schedule in use in many countries was established more than 25 years ago. Since then, the epidemiology of infectious diseases has changed, new vaccines have been introduced, health services have evolved, and other interventions have been linked to traditional EPI activities. In addition, much has been learnt about the mechanism of action and impact of vaccines. Given these developments, it is recognized that new or alternative schedules may be desirable to optimize impact, although available evidence suggests that a single immunization schedule would not suit all countries.

IVR therefore embarked on a project to determine how best to design a vaccination schedule at country level based on costs, implementation and delivery, disease burden and vaccine responses by age and number of doses. Progress during 2008–2009 is summarized as follows.

A global network of collaborators on immunization schedules was constituted, comprising 12 academic institutions and research centres worldwide.* At its first meeting in September 2008, the network agreed to develop an evidence-based platform for optimal immunization schedules with a focus on developing standardized methodologies, a research agenda to address critical research questions, and a framework for national decision-making, particularly in low- and middle-income countries.

Research agenda: In order to help define the key questions and study designs required to fill any gaps in evidence and to assess the potential of alternative schedules, it was decided to: (a) analyse and summarize all previous reviews on immunization schedules for the selected vaccines; (b) establish a preliminary list of research questions relevant to schedules for each vaccine as a first step to identify

* Core members of the Steering Group are the Agence de Médecine Préventive, France; Bocconi University, Italy; the Institute of Child Health, United Kingdom; the London School of Hygiene and Tropical Medicine, United Kingdom; the University of Bern, Switzerland; and WHO.

further studies; and (c) make initial contact with two vaccine producers to explore their interest in supporting such studies.

Systematic reviews: Full systematic reviews of the evidence relevant to schedules for pneumococcal conjugate vaccines (PCV) and *Haemophilus influenzae* type b are in progress. In addition, a rapid review of the evidence on paediatric schedules for pertussis vaccines was presented to SAGE in 2009 under the auspices of its Pertussis Working Group, and a systematic review of rotavirus mortality data in infants initiated, finely stratified by age during the first two years of life.

A SAGE Working Group on Optimizing the Use of Conjugate Vaccines facilitated the publication of a concept paper published in *Vaccine*.¹³ The paper reviewed the current evidence on the immunogenicity, effectiveness and public health impact of different conjugate vaccine schedules. The authors conclude that, to maximize the public health impact of immunization programmes with these vaccines, consideration must be given to the role of indirect effects, alongside direct protection. A range of schedules and strategies were likely to be effective and further studies should look at the cost-effectiveness and programmatic feasibility of the different options. Two alternative schedules were tabled for further investigation.

Mathematical modelling and cost-effectiveness studies: In order to predict the impact of various schedules, the dynamic age-structured model for PCV is being adapted to the dynamics of transmission in low- and middle-income countries. To collect key data for this model using a standard format, discussions took place during 2009 with researchers in Burkina Faso, the Gambia, Israel, Kenya, Thailand and Togo, as well as with the Pan American Health Organization. The opportunity was also taken to collect information on other priority vaccines of the project. A review of published mathematical models and cost-effectiveness analyses for PCV and rotavirus were also carried out, supplemented by expert reviews, to identify the key parameters that impact the two vaccines.

Translation: To apply the project strategy to the selected vaccines and to context-specific scenarios, collaboration was initiated with EPIVNet, a WHO project to promote evidence-informed policies at country level, as well as with SIVAC, an initiative to strengthen national immunization and vaccine advisory committees. Negotiations were also initiated with several vaccine and disease expert groups worldwide. Input is regularly obtained from WHO regional colleagues to ensure implementation at country level.

In commending the progress of the project at its meeting in October 2009, SAGE noted that the data needed to design immunization schedules should include regulatory requirements, the characteristics of the target populations and other concomitant or sequential immunizations. Moreover, the costs associated with any

change to immunization schedules should not be underestimated, nor the need for their regular updating.

2.3.4 Immunization coverage and gender balance

With a view to examining the link between gender and immunization coverage across countries, IVR convened a meeting of the ad hoc Advisory Committee on Gender and Immunization on 15 September 2009. Spearheaded by the GAVI Alliance, the Committee defined a project protocol to collect the evidence and current state of knowledge on this issue and, following an open call for proposals, the study was commissioned. It is expected that the results of the analysis will be submitted to SAGE in November 2010.

2.4 IVR advisory committees

2.4.1 IVR Vaccine Advisory Committee

The IVR Vaccine Advisory Committee (IVAC) was established in 2001 to provide advice on the strategic direction of IVR, review progress and promote synergies among the key players in vaccine R&D. The group met twice during 2008–2009, during which major research topics reviewed were influenza activities; cost–effectiveness models for decision-making at country level; capacity strengthening; vaccination beyond infancy; and revised immunization schedules. IVAC also provided guidance on the IVR Strategic Plan 2010–2020.

Pandemic influenza activities became a significant focus for the IVR team. IVAC was regularly briefed on the influenza vaccine technology transfer project to build production capacity in developing countries and create a technology platform to assist the transfer of an IPR-free technology package. Discussion focused on the choice of technologies, quality assurance, oversight, costs and IVR's role in the process. IVAC commended the progress made and approved the technology hub option.

Regarding cost–effectiveness tools, it was agreed that training for potential users of vaccine decision-making tools was urgent, and should involve academia and the relevant ministry of health. IVR would focus on improving the quality of data and interpretation of results, and standardizing tools. Practical guidelines on collecting costing information and cost-of-illness studies would be considered. Other challenges were to ensure that all data from economic evaluations were integrated in a transparent manner into broader interventions.

Capacity strengthening was recognized as an inherent feature of IVR activities, particularly related to clinical trial capacity in developing countries. IVAC recommended that, to improve the visibility of IVR efforts in this area, the success stories from the meningitis, pandemic influenza, measles aerosol and other vaccine projects be pulled together into a compelling advocacy presentation.

The project to expand vaccination beyond infancy was considered high priority new research. IVR will develop the research agenda for implementation by stakeholders as

appropriate. It would be important to learn from vaccination in younger adults, which may enlighten an eventual policy for the elderly, and to focus on gathering data in the developing world.

Other topics presented to IVAC were the review of immunization schedules for their optimum effectiveness, operational ease and cost, particularly in the light of potential new vaccines. IVAC considered the project useful, relevant and timely and encouraged continued focus in this area. Initial studies on the prioritization of vaccine-preventable diseases were also discussed.

Regarding the Strategic Plan 2010–2020, members noted that the strategic functions were coherent and aligned with the recent research and innovation policies of WHO. Several recommendations were made on elements of the Plan, notably the need for monitoring and evaluation, and to focus on high-impact public health projects that will facilitate access to health technologies in developing countries. These and other valuable comments on the IVR functions, focus and partnerships, were used to develop the final publication.

2.4.2 Advisory Committee on Dengue and other Flavivirus Vaccines

The Advisory Committee on Dengue and other Flavivirus Vaccines guides WHO on the development and evaluation of new vaccines against dengue and Japanese encephalitis (JE), and reviews important developments in relation to other flavivirus vaccines such as those against tick-borne encephalitis, West Nile and yellow fever. Annual meetings were held in Belem, Brazil (2008) and Geneva, Switzerland (2009), during which the Committee reviewed early stage dengue vaccines, and lead dengue and JE vaccine candidates and made specific recommendations to WHO and the manufacturers. In addition, members agreed on the need for updated written standards for the production and quality control of dengue vaccines, and these are now in preparation.

2.4.3 Diarrhoeal and Enteric Diseases Vaccines Advisory Committee

The Advisory Committee on Diarrhoeal and Enteric Diseases Vaccines guides the global strategic plan and research agenda for the development and introduction of safe and effective vaccines against the main pathogens that cause diarrhoeal and enteric diseases. The Committee also recommends roles that IVR might play in specific projects or undertakings. At its meetings in 2008 (Geneva, Switzerland) and 2009 (Málaga, Spain), members:

- drew up a global research agenda for enteric vaccines, based on their status of development, covering developmental, introduction and operational studies (e.g. to understand why vaccine efficacy is lower in developing country settings for orally delivered enteric vaccines);
- recommended future IVR research priorities for enteric vaccines and mucosal immunization and potential collaborative projects and sources of funding;

- provided a detailed analysis on the results of the rotavirus clinical studies in Africa and Asia to facilitate a SAGE policy update; and
- supported the ad hoc working groups on typhoid and cholera to assist SAGE in its recommendations on these vaccines.

2.4.4 WHO–UNAIDS HIV Vaccine Advisory Committee

The WHO-UNAIDS HIV Vaccine Advisory Committee comprises leading experts in basic science, HIV vaccine R&D, clinical research and trial design, regulatory and ethical aspects, as well as community representatives. The Committee enjoys dynamic interaction with all global HIV vaccine stakeholders and with IVR via regular teleconferences. In 2008–2009, two meetings were organized in Patthaya, Thailand and Stockholm, Sweden respectively. The scientific briefings at these meetings reviewed results from the STEP and Phambili recombinant Adeno5 phase IIb clinical trials; an assessment of potential vaccine-induced susceptibility to HIV; progress with the Thai RV144 efficacy trial; the role of mucosal immunity for vaccine protection; and safety issues related to the conduct of vaccine trials and immunization programmes in areas with high prevalence of HIV.

The Committee also provided technical advice on two clinical trial protocols to be conducted in Thailand and the United Republic of Tanzania, and issued recommendations and policy statements for national authorities and decision-makers on announcing the results of the RV144 vaccine trials.

2.4.5 Advisory Committee on Human Papillomavirus Vaccines

The Advisory Committee on HPV vaccines reviews advances with these vaccines and related matters such as the potential integration of cervical cancer screening and treatment (secondary prevention) into national immunization programmes. The primary focus of the Advisory Group meeting in May 2008 was a presentation to SAGE of evidence that could support the first ever recommendation on this new type of vaccine. Members thus reviewed new data that would be critical for a WHO policy on HPV vaccines, including clinical efficacy, cost-effectiveness, delivery mechanisms, financing and regional needs. Recommendations were also made on monitoring HPV vaccination programmes, especially for low- and middle-income countries; the role of the WHO HPV Laboratory Network in such monitoring; and priority research needed to support decision-makers on the introduction of HPV vaccines. Finally, members provided comments on the recent WHO/UNFPA HPV Vaccine Work Plan.

2.4.6 Global Action Plan for Pandemic Influenza Vaccines Advisory Group

To oversee implementation of the Global Action Plan to Increase the Supply of Influenza Vaccines (GAP), an Advisory Group was formed of representatives from industrialized and developing countries, with and without manufacturing capacity. The Group met for the second time in November 2008¹⁴ to review recent progress in the field and action taken by the IVR Secretariat to implement the Group's recommendations. Members made the following comments.

2.4.7 Malaria Vaccine Advisory Committee

Increased use of seasonal influenza vaccine. More data should be gathered in developing countries on the disease burden and economic impact of seasonal influenza. This would allow countries to review the cost-effectiveness of annual influenza vaccination and may increase demand. It was also recommended that a new survey of country policies on seasonal vaccine be conducted, and high-level political awareness stimulated. To this end, the World Health Assembly resolution on seasonal influenza vaccination should be refreshed to reinforce the link between seasonal vaccine use and pandemic vaccine availability. IVR should work with the WHO Global Influenza Programme to make this happen.

Production capacity for pandemic vaccines. Members considered that production capacity be increased further and sustained irrespective of seasonal vaccine use; that technology transfer to developing country vaccine manufacturers should continue; and that the GAP business plan¹⁵ be published to allow analysis of its assumptions and results.

R&D into new technologies. The Group applauded the antigen-sparing observed with new adjuvants and technologies, and encouraged initiatives to study correlates of protection. Discussion focused on challenges in epidemic influenza vaccination due to antigenic drift of circulating viruses, and to the need for boosters to induce protective immunity. Members recommended more research to improve seasonal vaccines that can induce broad spectrum immunity and efforts to increase access to new technologies, which will need strengthened collaboration with regulatory authorities.

Regarding the H5N1 vaccine stockpile, the group requested that any modelling exercise be reviewed regularly so that modifications can be made in line with advances in technology.

The IVR Malaria Vaccine Advisory Committee provides guidance and oversight on activities related to malaria immunization prior to the phase III trial stage. The primary focus of the Committee is to spearhead activities that enhance understanding of the science and knowledge on evaluation of candidate malaria vaccines. In 2008–2009, the Committee provided further consensus-based guidance on methods to measure malaria vaccine efficacy in field trials (see 4.3.4). In addition the Committee held a technical consultation in June 2009 on progress and challenges for whole organism malaria vaccines in endemic countries.¹⁶ The Committee also published a consensus guidance document on evaluation of *P. vivax* vaccines in endemic countries,¹⁷ a timely publication given the shift in emphasis towards *P. vivax* by some stakeholders. Also facilitated by IVR was the development of a comprehensive framework to maximize the utility of data generation in malaria vaccine field efficacy trials.

2.4.8 IVR/Global Malaria Programme Joint Technical Expert Group

In April 2009, IVR and the WHO Global Malaria Programme established a Joint Technical Expert Group (JTEG) on malaria vaccines entering pivotal phase III trials and beyond. The group advises WHO on activities related to malaria vaccines at this later stage of development, specifically on clinical trial data necessary to evaluate public health impact in malaria endemic countries; and on the design, conduct, analyses and interpretation of trials in phases I-IV. The advice of JTEG enables WHO to formulate policy recommendations through SAGE.

The first JTEG meeting took place in June 2009. Members recommended that, provided efficacy results from the RTS,S/AS01 phase III trial were satisfactory and that the vaccine is registered and prequalified, data to allow consideration of a WHO policy recommendation should be available by 2015–2016. Such a policy recommendation would take into consideration, inter alia, efficacy results after 30 months of follow-up per child in the current phase III trial, and the cost-effectiveness of RTS,S as an additional tool to existing control measures.

For more information, visit www.who.int/vaccine_research/jteg/en/index.html.

2.4.9 Advisory Committee on Quantitative Research in Immunization

The Advisory Committee on Quantitative Research in Immunization (QUIVER) advises IVR on research related to the estimation of burden of vaccine-preventable diseases, modelling the impact of vaccine interventions, economic evaluations of vaccine interventions and other analytic components of implementation research. The Committee has 12 members that cover the wide range of skills required.

At its meetings in October 2008 and 2009, the Committee reviewed the burden of measles, tetanus and pertussis; the methods used for WHO/UNICEF estimates for national immunization coverage; modelling of vaccine interventions for measles and pandemic influenza; post-polio eradication modelling; and economic and health systems impact of measles eradication. The advice and recommendations of QUIVER serve to prepare evidence-based background papers for IVR.

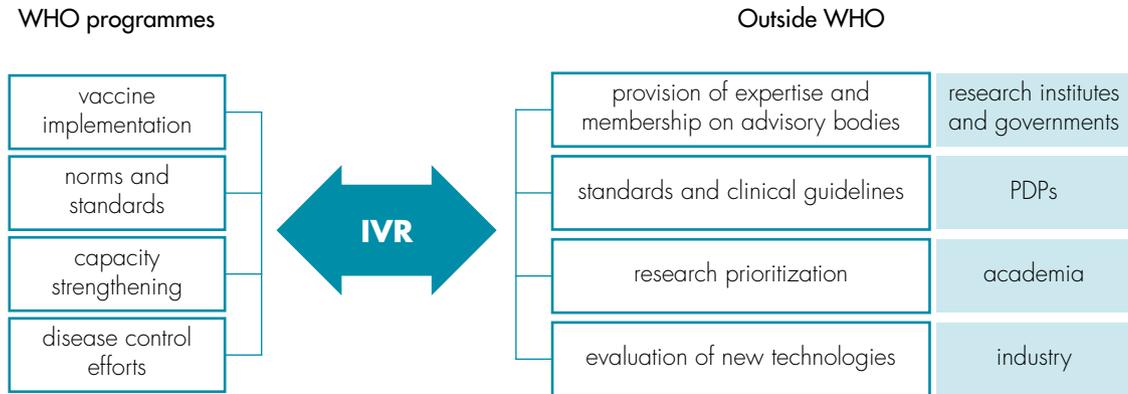
2.5 IVR in partnerships

2.5.1 Overview

Sharing responsibilities to move the vaccine R&D agenda forward is no longer an option, but an obligation. The number of entities supporting the field, whether disease focused, evidence-oriented or financial partners, is ever increasing. So must the level of coordinated action.

IVR continued to enjoy close collaboration with all stakeholders in vaccine and vaccination research and product development, in both the public and private sectors (Figure 2). Its status as the WHO unified arm for vaccine research confers the credibility expected from Member States, research institutes, academia, global partnerships and initiatives, as well as the vaccine industry. Within WHO, IVR benefits from the expertise of its colleagues in programmes at headquarters, and

FIGURE 2. IVR INTERACTION WITH KEY STAKEHOLDERS



regional and country offices, supported by a network of collaborating centres and others such as the WHO Global Outbreak Alert and Response Network. In carrying out its mandate, IVR is an integral component of the Department of Immunization, Vaccines and Biologicals, with UNAIDS and the Special Programme for Research and Training in Tropical Diseases as its major constituents.

An example of IVR input to a new initiative, launched during 2008–2009, was the strategic advice provided to G-FINDER, a five-year initiative of the George Institute for International Health in Australia. The objective of the initiative is to collect comprehensive investment data on pharmaceutical products for 31 neglected diseases of the developing world, as evidence for policy-makers and funders. The G-FINDER reports, published in February and December 2009,¹⁸ provided broad, consistent and comparable data for these diseases for the first time along with an analysis of the investment challenges faced.

2.5.2 African AIDS Vaccine Programme

IVR has hosted the African AIDS Vaccine Programme (AAVP) since its inception in 2000 and most recently supported the implementation of the AAVP Strategic Plan 2007–2011 in the areas of advocacy, policy development, networking and capacity strengthening.

High-level advocacy for HIV vaccine R&D was achieved by the AAVP High Representative, Mrs Jeannette Kagame, First Lady of Rwanda. In June 2008, Mrs Kagame hosted an event at the United Nations Special Session on HIV/AIDS in New York, attended at the highest diplomatic and ministerial levels, during which participants endorsed the new AAVP Strategic Plan. In September 2009, Mrs

Kagame hosted another advocacy session at the WHO Regional Committee for Africa, where she presented the Abuja Declaration and progress on the AAVP transition to self-governance in Africa. Several ministers of health pledged to explore political and financial support for the AAVP.

In December 2009, IVR organized the fifth AAVP Forum in Kampala, Uganda with wide cosponsorship from international partners* and attendance by more than 350 participants, largely from the African continent. The overall theme of the Forum – Africa needs an AIDS vaccine: building common platforms for HIV prevention research in Africa – covered the status and challenges of HIV vaccine R&D; capacity building to conduct vaccine trials in Africa; and policy, regulatory, legal, ethical and access issues. Recommendations and action points for the AAVP and its partners for the coming two years served to develop the Kampala Call for Action.

The AAVP in transition. Following an external evaluation, and recommendations from the fourth AAVP Forum in Abuja, it was agreed that the AAVP should be housed within an African institution. To address the complex transition from WHO supported administration, an independent AAVP Transition Advisory Panel was established to oversee the process of selecting a new host institution. Following a thorough review of applications, including a final anonymous ballot, the Uganda Virus Research Institute in Entebbe, Uganda was announced as the selected institution at the fifth AAVP Forum. An AAVP Business Plan and Memorandum of Understanding will be finalized in early 2010 and potential resources identified to support the AAVP transition to Africa.

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

2.5.3 Global HIV Vaccine Enterprise

The Global HIV Vaccine Enterprise (GHAVE) is an alliance of independent organizations committed to accelerating the development of a preventive HIV vaccine based on a shared scientific strategic plan. GHAVE is applying novel paradigms to harness scientific opportunities for HIV vaccine development. During the biennium, this included commitment to the AAVP transition to Africa and organization of a Coordinating Group on Preparation for Communication of HIV Vaccine Efficacy Trials. IVR contributed to the new GHAVE Scientific Strategic Plan and co-organized regional networking and advocacy meetings, including a regional consultation on the creation of an AIDS Vaccine for Asia in February 2009 in Beijing, China.

For more information, visit www.hivvaccineenterprise.org.

* Gates Foundation, GHAVE, IAVI, Karolinska Institute, NIH, UNAIDS, US Walter Reed Army Institute of Research, and Wellcome Trust.

2.5.4 AIDS Vaccine for Asia Network

With 61% of the world's population, Asia is at an elevated risk of an accelerated HIV epidemic. Complex patterns such as the high genetic variability of HIV strains and the diverse genetic background of the host populations will have a major impact on HIV vaccine efficacy and future use in the region. Collectively, countries in Asia have significant vaccine R&D capacity, having conducted over 20 clinical trials involving around 20 000 subjects. Today, it is clear that united efforts across nations are needed to produce, refine and evaluate the next generation of HIV vaccine candidates. Collaborative efforts, aligned with the goals of the Global HIV Vaccine Enterprise, have already borne fruit with the recently formed AIDS Vaccine for Asia Network (AVAN).

The mission of AVAN was discussed at a regional meeting convened by IVR with the Chinese AIDS Vaccine Initiative and GHAVE in February 2009 in Beijing, China, following which a concept paper for the AVAN Strategic Plan was finalized.¹⁹ Serving as a forum to promote regional expertise, capacity building and technical assistance, AVAN will endeavour to expand preclinical and clinical trials and enhance regulatory and manufacturing capacity to accelerate the development of AIDS vaccines in Asia.

For more information, visit www.avan.asia.

2.5.5 Pediatric Dengue Vaccine Initiative

IVR is a partner and Board member of the Pediatric Dengue Vaccine Initiative (PDVI), which aims to accelerate the development of dengue vaccines and plan for access to the vaccines when they become available. Areas of collaboration relate to awareness efforts and the development of regulatory standards, the prediction of vaccine impact through health economical studies, modelling of transmission, and the development of scenarios for immunization strategies. In addition, 2009 saw the publication of the third edition of dengue guidelines for diagnosis, treatment, prevention and control,²⁰ recommending a simplified case classification system as a result of a large-scale clinical prospective cohort study coordinated by the Special Programme for Research and Training in Tropical Diseases.

For more information, visit www.pdvi.org.

2.5.6 Human papillomavirus vaccine partnerships

IVR, PATH, the International Agency for Research on Cancer and Harvard University have been collaborating in a five-year programme initiated in 2005 and funded by the Gates Foundation to accelerate the introduction and use of HPV vaccines. IVR facilitated policies for vaccine use; standards for laboratory reagents and methods; establishment of the global HPV laboratory network; and the global database of information on HPV. The partnership has been highly effective because the efforts of the individual partners, together, inform WHO policy and the guidance that countries

expect from WHO. The database, developed in collaboration with the Catalan Institute of Oncology in Barcelona, Spain is accessible to WHO Member States through the WHO/Institut Català d'Oncologia Information Centre.

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

2.5.7 Measles Aerosol Vaccine Product Development Group

In 2002, IVR, the US Centers for Disease Control and Prevention and the American Red Cross established the Measles Aerosol Project to develop and license a device and vaccine to administer measles vaccine by aerosol. IVR manages the project and ensures participation of the best technical experts. The aerosolized vaccine will allow administration by non-medically trained personnel and avoid injection-related safety problems, especially in resource-poor settings and during vaccination campaigns. The project, funded by the Bill & Melinda Gates Foundation, has made substantial step-wise progress towards its goal: phase I clinical trials were completed in 2008 and the phase II/III pivotal trial started in 2009. The vaccine is expected to be registered as early as 2011 (see Section 3.1.1 for details of progress during 2008–2009).

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

2.5.8 Meningitis Vaccine Project

The Meningitis Vaccine Project (MVP) is a partnership between WHO and PATH to eliminate meningitis as a public health issue in sub-Saharan Africa through the development, testing, introduction, and widespread use of a conjugate meningococcal vaccine. IVR continued to ensure smooth collaboration among all partners which enabled the successful conduct of vaccine trials in Africa and India to international standards (see Section 3.1.2 for MVP activities during 2008–2009). In addition, the overall capacity of the sites to conduct the vaccine trials was comprehensively enhanced, including the development of standard operating procedures and adherence to good clinical practices, the ability to implement pharmacovigilance surveillance and reporting, laboratory capacity for serological testing of vaccine antigens, improving the knowledge and expertise of scientists in vaccine development, and awareness of the complexity of ethical issues surrounding clinical research. The capacity of the national regulatory authorities to authorize and inspect the clinical trials was also enhanced, particularly by using the project as a case study during the training.

For more information, visit www.meningvax.org.

2.5.9 African Meningococcal Carriage Consortium

Following the successful launch of a large multi-centre African Meningococcal Carriage Consortium “MenAfriCar” under the leadership of the London School of

Hygiene and Tropical Medicine, London, United Kingdom, carriage studies with the meningococcal A (MenA) conjugate vaccine are being conducted in eight sites in the sub-Saharan meningitis belt.* These studies, funded by the Wellcome Trust, the Bill & Melinda Gates Foundation and the Research Council of Norway, will allow an evaluation of the vaccine effect on carriage and transmission.

For more information, visit www.menaficar.org.

2.5.10 Global Partnership to Stop TB

IVR continued to house the secretariat of the Working Group on New TB vaccines of the Global Partnership to Stop TB. The Working Group comprises Stop TB partners from academia, public sector product development, the vaccine industry, regulators and public health experts, and has a governing body and five task forces that serve as the operational arms of the group. The key achievements of the Working Group during 2008–2009 were:

- the development of advocacy materials targeting remote and/or poorly literate communities where tuberculosis (TB) vaccine clinical trials will take place;
- support to a network of TB vaccine clinical trial sites that shares information and assists clinical staff at field sites intending to conduct TB vaccine trials;
- consensus on how to advance live TB vaccines (recombinant BCG and attenuated *M. tuberculosis*) in clinical trials;²¹
- creation of a programme to increase regulatory capacity for TB vaccine development in endemic countries, particularly through collaboration with the African Vaccine Regulators Forum and the Developing Countries' Vaccine Regulators Network; and
- initiation of a comprehensive survey of TB vaccine candidates and update of the TB Vaccines Pipeline document.²²

* Burkina Faso, Chad, Ethiopia, Ghana, Mali, Niger, Nigeria and Senegal.

3

Research and
product development

3.1 Product development

3.1.1 Measles aerosol vaccine

IVR has been collaborating with CDC and the American Red Cross since 2002 to develop and license a device and vaccine to administer measles vaccine by aerosol. All non-clinical studies, i.e. device characterization, the standardization and validation of the ELISA Ig G and PRNT measles tests,²³ and animal safety, efficacy and GLP toxicology studies²⁴ have now been successfully completed.

Three aerosol delivery devices were selected from almost two dozen for evaluation in phase I safety and immunogenicity trials in India. Each device was assessed with respect to the character of the aerosol as well as criteria that address practicality/field usability and cost per dose delivered.²⁵ A panel of experts reviewed information on the three devices, including their performance characteristics, vaccine potency retention during nebulization, results from the phase I trial and field usability. One was selected for the phase II pivotal trial in India.

In 2007, a phase I clinical trial of the measles aerosol vaccine in 145 healthy measles immune volunteers of 1–35 years of age was completed in three different sites in India. The vaccine was found to be safe, well tolerated and immunogenic (WHO unpublished data). In 2009, the phase II/III pivotal trial of the vaccine was initiated in healthy infants of 9–12 months of age who were eligible for their first measles vaccination, using the selected device. The study design is a randomized, open-label, active-control, parallel group, non-inferiority trial. The same dose is being administered by aerosol and by subcutaneous injection (the currently licensed route of inoculation). A total of 2000 infants are being enrolled in the study, randomized 1:1 to the two arms (aerosol 1000; subcutaneous 1000). A subset of 100 subjects per arm will be followed to day 364 to obtain additional safety data. Blood samples for assessment of the post vaccination levels of anti-measles antibody are being collected.

Focus groups were conducted in Guyana, Mexico and Oman to inform the final device configuration, along with further field evaluations to complement those conducted in India (planned in Africa and Asia in early 2010 using the final device configuration). Discussions are ongoing to prepare for scaling up the manufacture of the final device and, to this end, a preliminary outline of technical and financial requirements have been discussed with the device manufacturer. The IND dossier will be completed upon the results of the phase II trial and regulatory information on the final device configuration.

3.1.2 Meningococcal conjugate vaccine

The goal of the WHO-PATH Meningitis Vaccine Project (MVP) to develop and introduce a meningococcal conjugate vaccine for use in the sub-Saharan African meningitis belt is nearing reality. Research over the last two years is summarized below.

SUPPORT TO CLINICAL DEVELOPMENT

Studies in the population group 1–29 years of age

The *pivotal phase II* study was successfully completed with the follow-up of toddlers up to two years after a single vaccine dose (PsA-TT, meningococcal A (MenA) conjugate vaccine) at two sites within the meningitis belt – one rural (Basse, the Gambia) and one urban (Bamako, Mali). The vaccine was safe, immunogenic, and induced immune memory and a persistent antibody response in healthy African toddlers. Immune responses at all time points were found to be superior to those induced by the licensed polysaccharide vaccine. In addition, the PsA-TT vaccine had a boosting effect in antibody concentrations against tetanus.

The *phase II/III* trials were subsequently completed successfully at three sites in the meningitis belt (the Gambia, Mali and Senegal) and one in India (Vadu district in Maharashtra). Results from the pivotal trial in toddlers were confirmed among subjects 2–29 years of age at all sites. The vaccine was safe and superior to the licensed polysaccharide vaccine in terms of immunogenicity and antibody persistence. Tetanus antibody boosting was also confirmed.

Preparation and planning were undertaken for the launch of *phase III/IV* trials in India and in Africa. Sites were selected and trained, and study protocols and documents were developed and finalized after extensive peer review. Final ethical and regulatory clearances were granted for two studies to start in early 2010: a lot consistency trial in Indian children and a wide safety study in Africa among the entire target population 1–29 years old.

Studies in the infant population

A *phase II* infant study protocol was finalized after extensive peer review and ethical and regulatory clearance processes. The study was launched in November 2008 at the Navrongo Health Research Centre in Ghana to assess the safety and immunogenicity of two regimens of the MenA conjugate vaccine MenAfriVac™: (a) 2.5 µg, 5 µg, and 10 µg doses given in two doses at 14 weeks and at 9–12 months old; and a single 10 µg dose given at either 9–12 months or at 12–18 months old and administered concomitantly with EPI vaccines. A total of 1200 subjects have been enrolled in the study and will be followed up to age 3. Results will inform the recommendations for infant immunization with MenAfriVac™.

SUPPORT TO VACCINE LICENSURE AND INTRODUCTION

Vaccine licensure and prequalification

Vaccine licensure of MenAfriVac™ for use in 1–29 year olds was granted in January 2010. It is expected that the WHO prequalification process will be completed in July

2010, and the vaccine introduced in Burkina Faso, Mali and Niger in late 2010. In anticipation of this vaccine availability, the MVP partnership developed an Investment Case for submission to the GAVI Alliance. IVR coordinated this paramount effort, ensuring adequate and timely contribution from all experts, partners and stakeholders.

The Meningitis Investment Case

The introduction strategy of the MenA conjugate vaccine was presented as an Investment Case to the GAVI Alliance in June 2008. This strategy seeks to eliminate rapidly the group A meningococcal (NmA) meningitis epidemics that have been a devastating public health problem in sub-Saharan Africa for the past 100 years. The introduction of the vaccine through mass campaigns and routine immunization will provide, within the first five years of widespread use, long-term protection to approximately 400 million people and prevent 140 000 deaths and 300 000 disabilities. Furthermore, an estimated US\$ 121 million will be saved in diagnosis and treatment costs. The proposed activities will also reduce non-epidemic NmA meningitis and improve response to epidemic meningitis. The Investment Case comprises the following four components.

- Preventive MenA conjugate vaccine introduction involves immunizing 250 million 1–29 year olds and 23 million infants in up to 25 GAVI-eligible African countries by 2015. The effort should protect up to 400 million people through herd immunity.
- To ensure that adequate quantities of meningococcal polysaccharide (MenP) vaccines are available, epidemic response centres and stockpiles will be established and the timeliness of response improved. This is important to ensure a smooth transition from current epidemic response strategies to a preventive approach, and to respond to the threat of non-NmA meningitis outbreaks (C or W135).
- The third component will strengthen the enhanced surveillance system of meningitis, establish case-based surveillance, guide the introduction of MenA conjugate vaccine through risk assessment, monitor meningitis epidemiology, and document the impact of the vaccine on epidemic NmA meningitis.
- Country-level capacity-building will ensure that adequate national and regional capacity exist to implement the plan.

The GAVI Alliance Board approved US\$ 370 million for the Meningitis Investment Case strategy, and a further US\$ 182 million representing country co-payments. In September 2008, through the Yaoundé declaration, ministries of health of the African meningitis belt countries demonstrated their commitment to co-finance the project, and in November 2008 the GAVI Alliance approved US\$ 29.5 million for MenA vaccine introduction in Burkina Faso, Mali, and Niger in 2010.

In June–July 2009, the Ministry of Health of Burkina Faso, in collaboration with IVR, organized a workshop in Bobo Dioulasso to elaborate the introduction plan. This was followed in September 2009 by a workshop in Ouagadougou that detailed a template of district and regional micro plans. These tools have now been validated and each district and region is currently conducting the micro planning exercise with national and IVR support. The National Plan and budget should be finalized by February 2010. In parallel, a detailed logistic plan is being drafted.

Mali and Niger have also started preparing to introduce the new vaccine and have drafted introduction plans which will be discussed during forthcoming national workshops.

3.1.3 New technologies: vaccine delivery systems

Research on the intradermal delivery of vaccines with needle-free technologies was carried out to determine whether this route is able to permit dose-sparing, and whether the disposable cartridge jet injectors can simplify vaccine administration. A number of clinical trials were conducted under the auspices of IVR, the WHO Polio Eradication Initiative, CDC and PATH to evaluate a reduced-dose inactivated polio virus vaccine in Cuba, India and Oman, and a reduced-dose influenza vaccine in the Dominican Republic. The results from the polio studies conducted with different vaccines and delivery devices varied from study to study. One study achieved a five-fold reduction in vaccine dose with intradermal administration; a second suggested that dose-sparing may depend on the source of the vaccine, and a third study postulated that device optimization was required. IVR and PATH are now developing a broader vision of topical and intradermal delivery.

3.1.4 Post-exposure rabies prophylaxis in humans

An estimated 55 000 deaths from endemic canine rabies occur in Africa and Asia each year, yet the disease remains neglected in most countries in these continents. To address the increasing demand for post-exposure prophylaxis, IVR has been involved in a project with WHO Collaborating Centres in the American and European regions to develop and assess unique and highly efficacious mouse monoclonal antibody cocktails. Following extensive research,²⁶ two novel combinations that could be less expensive alternatives for passive prophylactic use to prevent the development of rabies in humans, particularly in developing countries, are under development with a vaccine manufacturer in India. Initiation of clinical development is envisaged for 2010.

3.2 Capacity strengthening

3.2.1 Overview

All IVR research projects comprise a capacity strengthening component to ensure that the staff involved – whether field workers, nurses, pharmacists, clinicians, manufacturers, laboratory staff, statisticians or ethical and regulatory authorities – are able to carry out their work to the highest international standards. Some capacity strengthening activities are highlighted elsewhere in this report, such as the

training workshop on methodology for molecular epidemiology studies, sequencing and phylogenetic analyses for HIV, or preparing national regulatory authorities to authorize the clinical trials of meningococcal vaccines. Further examples are provided below.

3.2.2 Ethical and regulatory capacity for HIV clinical trials

During 2008–2009, the WHO/UNAIDS document on *Ethical considerations in biomedical prevention trials* became available in six languages. The document provides recommendations and decision-making frameworks on complex ethical issues that are often major challenges in preparing and conducting clinical trials, with a special emphasis on perspectives from low- and middle-income countries with a high burden of HIV.

To facilitate implementation of the document, IVR developed training modules for practical application and use by ethics committees, national regulatory authorities, principal investigators and community representatives. The French and English training modules were pilot tested at two workshops – one for French-speaking countries (January 2009, Dakar, Senegal) and the other for English-speaking countries (March 2009, Durban, South Africa). Participants agreed to test the modules in their own countries and provide feedback. The modules, along with support materials, will be published as a web-based training tool, and translated into Portuguese.

3.2.3 Training for developing country influenza manufacturers and regulators

Several specific training activities took place in the context of strengthening the capacity of developing country manufacturers to produce influenza vaccine. In November 2008, a theory and hands-on quality control workshop was held at the National Institute for Biological Standards and Control in the United Kingdom for IVR grantee country regulators. The same workshop was organized for the developing country manufacturers in April 2009 at the International Technology Platform for Influenza Vaccine in the Netherlands, followed by a three-week influenza vaccine production and cGMP workshop. These courses, as well as annual meetings of grantee manufacturers to learn from shared experiences, will be repeated in 2010.

3.2.4 Training of the Zanzibar Ethical Research Council for cholera vaccine study

Prior to the start of the cholera project in Zanzibar, United Republic of Tanzania, a training course was held for the Zanzibar Ethical Research Council. The biomedical ethics training was conducted in three stages over several months in collaboration with the Pan African Bio-ethics Network and the Special Programme for Research and Training in Tropical Diseases. The final stage comprised an external assessment from which it is expected that the Research Council will be certified by the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), and entered into the WHO database of recognized ethics review committees.

4

Implementation research

4.1 Research to translate evidence into policies and practice

4.1.1 Revised WHO position paper on rotavirus vaccines

As the research arm of the WHO Strategic Advisory Group of Experts on immunization (SAGE), IVR conducts detailed technical analyses and appraises the suitability of methods to inform the development of immunization policies. During the reporting period, the following technical background papers led to SAGE recommendations on vaccine use.

Based on a review of new information on the immunogenicity and efficacy of two oral rotavirus vaccines from trials in Africa and Asia (see Section 2.1.5), SAGE and the WHO Global Advisory Committee on Vaccine Safety considered that both vaccines were safe and effective in preventing gastrointestinal disease caused by rotaviruses. The WHO position paper on rotavirus vaccines²⁷ was thus revised and published in December 2009,²⁸ recommending that rotavirus vaccine for infants should be included in all national immunization programmes. In countries where diarrhoeal deaths account for $\geq 10\%$ of mortality among children aged < 5 years, the introduction of the vaccine is strongly recommended.

4.1.2 Policy framework for cervical cancer prevention

Cervical cancer is the leading cause of cancer in developing countries and the second leading cancer in women worldwide. In fact, more than 80% of the estimated 260 000 cervical cancer deaths in 2005 occurred in developing countries, where screening programmes are nonexistent or malfunctioning and where financial resources for treatment are scarce. IVR has been involved in the HPV vaccine field for many years, particularly through support to laboratory studies and the organization of forums to guide the field and assess global needs. By 2007, two producers had licensed HPV vaccines, both of which are now WHO prequalified vaccines.

During 2008–2009, a significant accomplishment was the generation of a policy on HPV vaccine. In November 2008, IVR prepared a detailed HPV Vaccine Background Paper, based on which SAGE made global recommendations on the policy framework and strategic options for the introduction of HPV vaccines in countries.²⁹ The biennium also saw the consolidation of the Global HPV Laboratory Network under the WHO team responsible for the quality, safety and standards for vaccines and biologicals.³⁰ The 10 centres of the network across the world are now providing assistance on DNA and antibody detection and training.

The success of the project was based on systematic collaboration among colleagues and partners that focus not only on immunization, but also on reproductive and adolescent health and cancer control. These harmonized efforts have also enabled a more integrated, strategic approach to cervical cancer prevention and control.

4.1.3 Evidence for cholera vaccination and control

Over the last decade, trends in the epidemiology of cholera have changed. Epidemics in sub-Saharan Africa, for example, are more frequent, larger and longer-

lasting, and variant strains of *Vibrio cholerae* that produce the classical cholera toxin are replacing the original strain in parts of Africa and Asia, causing a more clinically severe disease. In addition, a lower cost cholera vaccine has been developed specifically for easier administration in developing countries. Thirdly, more evidence is available on the economic burden of cholera and the efficacy, field effectiveness, acceptability, feasibility and cost-effectiveness of oral cholera vaccination, both in endemic and crisis situations. These elements justified a revision in the WHO recommendations on cholera vaccination, last issued by SAGE in 2001.

In October 2009, SAGE reviewed the background paper on cholera vaccines prepared by a designated IVR working group that developed a definition of endemic cholera as *the occurrence of faecal culture-confirmed cholera diarrhoea in a population in at least three of the past five years*. Based on the evidence presented, SAGE reached the following conclusions.

- Given the availability of two oral cholera vaccines (one prequalified and the other requesting prequalification status) and new data on their potential use, immunization with these vaccines is recommended in areas where the disease is endemic, and should be considered in areas at risk of outbreaks in conjunction with other prevention and control strategies.
- Vaccines can serve as an immediate response while longer-term, essential interventions such as safe water and sanitation are put in place.
- Cholera vaccines should be on the priority list for WHO prequalification to accelerate their availability in developing countries.

The revised SAGE recommendations for control of both endemic cholera and cholera outbreaks were published in November 2009.³¹

4.1.4 Position paper on typhoid vaccines

Despite its relatively low profile, typhoid fever afflicts at least 21 million people a year, 600 000 of whom die from the disease. Recent data confirm this significant burden of disease, particularly in countries of South-East Asia, predominantly among the young. Effective vaccines against typhoid fever exist, but are largely un- or under-used, despite large-scale projects that have demonstrated their efficacy and the feasibility of easily introducing them into the immunization programmes of developing countries.

Against this background and the deliberations of SAGE, a revised WHO position paper on typhoid vaccines was published in February 2008.³² In parallel to the signal that the WHO position paper provides to the vaccine industry and donor community, IVR provides technical guidance to Member States on the potential introduction of typhoid vaccines (see Section 4.2.3).

4.1.5 Use of licensed H5N1 influenza vaccines in the interpandemic period

In October 2008, SAGE established a Working Group to examine the available evidence for the potential use of licensed human H5N1 influenza vaccines in the interpandemic period. Following a thorough review of published and unpublished data covering nine distinct parameters, SAGE made the following recommendations to the WHO Director-General at its meeting in April 2009.³³

Vaccination was strongly recommended for laboratory workers specifically involved in higher-risk activities such as large-scale production or manipulation of the virus. At a second level, vaccination was recommended for workers involved in a first response to H5N1 outbreaks and for health-care workers who manage H5N1 patients. In all other cases, the risks and benefits associated with H5N1 vaccination should be evaluated before it may be made available. Moreover, given the very low risk of infection in the general public in countries affected by the virus, vaccination was not recommended in this group without evidence of a particular risk.

Holders of licensed H5N1 vaccine were encouraged to gain experience with its use and expand knowledge on safety, immunogenicity, cross-reactivity, priming potential and duration of immunity in order to inform public health policies. SAGE made recommendations on studies that might be carried out in target groups in the context of postmarket surveillance. SAGE also considered that its initial recommendation on the size of the H5N1 vaccine stockpile remained appropriate, i.e. 50 million doses to complement rapid containment operations in the event of human-to-human transmission of H5N1, and 100 million doses for equitable distribution to low- and middle-income countries to help maintain the services considered most essential.

4.2 Support to vaccine introduction in countries

4.2.1 Operational research for cholera vaccine

A large-scale operational research study of cholera vaccine, supported by the Bill & Melinda Gates Foundation through IVR, began in Zanzibar, United Republic of Tanzania at the beginning of 2008 in collaboration with the Ministry of Health and Social Welfare of the Government of Zanzibar, the International Vaccine Institute and the Swiss Tropical and Public Health Institute.

As part of this, an effectiveness study was carried out with 100 000 doses of Dukoral® (the only prequalified cholera vaccine available in 2008) to vaccinate urban and peri-urban areas with a cholera rate of at least 1 case per 1000 population (approximately 50 000 people who are 2 years or more and not pregnant). The mass vaccination campaign was organized by the Zanzibar EPI with technical support from IVR. The two rounds of the campaign conducted in January and February 2009 achieved an overall two-dose coverage rate of 58.5%. Surveillance for the case-control study started in March 2009 to determine the “real life” vaccine effectiveness, including herd immunity. Interim results indicate that there will be a sufficient number of cases to determine effectiveness after one year, and that

interesting information may be obtained about interaction with water and sanitation measures. The final study results are expected in 2010.

In addition, the impact of pre-emptive vaccination in an endemic situation was explored to generate a better understanding of (a) acceptability and cost-effectiveness of the vaccine; (b) the feasibility of mass vaccination campaigns; and (c) the financial and logistic implications of a cholera vaccine stockpile. The Zanzibar study aimed to ascertain cholera vaccine acceptance and disease perceptions among households, health-care providers, community leaders and policy-makers. A study protocol with survey instruments were developed and implemented before and after the mass vaccination campaign to determine the distribution of categories of cholera-related experience. In order to gather data from different cultural settings, Kenya and the Democratic Republic of Congo were chosen to generalize results from Zanzibar to the African continent. Full results of the studies are expected in 2010.

Recent international interest in establishing a cholera vaccine stockpile for outbreak response led the project to examine possible mechanisms to finance and sustain such a stockpile; the impact of cholera vaccines as a complement to other control interventions, and the sociobehavioural implications of the use of cholera vaccines.

4.2.2 Introduction plans and strategies for human papillomavirus vaccine

Most developed nations have introduced the HPV vaccine, but in developing countries, where the disease burden is highest, access to the vaccine is limited due to its high cost. IVR has therefore been exploring, with partners such as the GAVI Alliance, the United Nations Population Fund and the International Agency for Research on Cancer, innovative ways to finance HPV vaccination programmes as part of a comprehensive cervical cancer prevention programme. For countries such as Bhutan and the United Republic of Tanzania that have already decided to introduce the vaccine, IVR has been supporting the development of their introduction plans and strategies.

4.2.3 Raising awareness of typhoid disease

Technical capacity is already stretched in typhoid-endemic countries. Thus, with a view to assisting countries interested in introducing typhoid vaccination, IVR, in collaboration with the International Vaccine Institute, is providing hands-on technical assistance and information on the disease, including country-specific epidemiological data and on available vaccines. Following the publication of the new WHO position paper on typhoid vaccination in 2008, a focal person was appointed to oversee typhoid activities, who initiated a comprehensive awareness-raising campaign among all stakeholders in typhoid-endemic regions on the value of typhoid vaccination. As a result, typhoid was placed on the agenda of significant national, regional and international forums, such as the high-level GAVI Forum in Hanoi, Viet Nam in November 2009.

IVR works closely with the International Vaccine Institute, the Delivery Team of the Bill & Melinda Gates Foundation and the Coalition Against Typhoid to ensure that countries can make evidence-based decisions on typhoid control. A report will be submitted to SAGE in 2010 on the opportunities, progress and challenges for activities related to typhoid fever. In this respect, the first ever guidelines on introducing typhoid vaccines for the control and prevention of typhoid in endemic countries are in preparation.

4.3 Norms and standards

4.3.1 Guidelines for the evaluation of dengue vaccines

Despite renewed efforts into vector control, dengue disease is still on the rise, as exemplified by a major outbreak in Brazil in 2008. To support the development of dengue vaccines, IVR published guidelines in 2008 for their evaluation in endemic areas.³⁴ The document makes recommendations on clinical trial primary and secondary endpoints, epidemiological requirements for field sites, and the long-term safety follow-up of vaccinees. The production and wide dissemination of the guidelines and an accompanying article³⁵ proved timely as the guidelines were seminal in the design of a large-scale proof-of-concept dengue vaccine trial launched in 2009 in Thailand. The guidelines have also informed regulatory authorities in the review of clinical trial applications, assisted vaccine trial sponsors and served as reference material for training. IVR monitors experience gained from ongoing clinical trials in order to update the guidelines as and when needed. The guidelines also serve as a basis for the efficacy and safety testing requirements in the new written standards on production, evaluation and quality control of live dengue vaccines.

4.3.2 Guidelines for enteric disease control and prevention

Regional rotavirus surveillance networks, comprising a growing number of countries, are now using the standardized generic protocol to monitor the burden of disease and standard operating procedures for specimen and data capture in the field. However, emerging regional reference laboratories have been using different methods and reagents for strain characterization, and several country laboratories wanting to conduct strain characterization have been unsure of which reagents and techniques to use. IVR therefore coordinated and facilitated the development of a laboratory manual³⁶ that describes the different characterization methods, provides standardized methods, techniques and reagents, and lists resources for obtaining the reagents for quality control and assurance. Technical advice is provided on which method may be most appropriate according to needs, capabilities and location (e.g. relative to circulating strains).

IVR also participated in the coordination and drafting of the generic protocol for monitoring the impact of rotavirus vaccination on gastroenteritis disease burden and for characterization of viral strains.³⁷

4.3.3 HIV assay standardization

IVR continued to encourage standardized laboratory assays for HIV vaccine research and clinical trials with a view to creating common platforms for the development of HIV vaccines suitable for use in developing countries. A summary of these activities is provided below.

Regulatory aspects and laboratory assays to measure HIV vaccine efficacy.

The technical report of a consultation on efficacy endpoints in HIV vaccine trials, published in *Vaccine*,³⁸ provides recommendations on validation and the role of viral load measurements, alone or in combination with other clinical assays, as surrogate markers for use in HIV vaccine efficacy trials.

Consortium on standardization of cryopreservation and HIV specimen repository.

This project, supported by the Bill & Melinda Gates Foundation in collaboration with Fraunhofer Institute for Biomedical Techniques, aims to develop, evaluate and standardize novel cryopreservation techniques for large-scale centralized storage of HIV-1 related specimens and reagents. The consortium has created optimized procedures, Good Clinical and Laboratory Practices for the process, and arranged shipment and storage of clinical specimens to ensure viability and reproducibility of laboratory assays used for HIV vaccine trials. In addition, the consortium arranged the transfer of cryopreservation technology to regional centres in developing countries, and organized two training workshops in 2008 and 2009 for young scientists from regional centres in Brazil, the Russian Federation, South Africa and Thailand.

Training in laboratory assays to measure T-cell and B-cell immune responses in HIV vaccine trials.

Capacity strengthening workshops were held on essential laboratory assays used in HIV vaccine trials. More than 50 scientists from developing countries were trained in HIV neutralization assays at a workshop held in Italy in collaboration with the Lund University (Sweden) and the San Raffaele Institute (Italy), and on measuring T-cell immune responses at two workshops organized in Johannesburg in collaboration with the National Institute of Virology, Johannesburg, South Africa and Duke University, Durham, USA.

Molecular epidemiology project. A survey was conducted and an extensive database established on the global spread and distribution of HIV-1 genetic subtypes and circulating recombinant forms (CRFs).³⁹ Integrating new epidemiology data published in 2009, the database was used to estimate the significance of various genetic subtypes and CRFs at the global, regional and country level between 1999 and 2008, and to assess dynamics and the role of different genetic variants of HIV in regional and sub-regional epidemics. Results of the analysis have been submitted to *The Lancet*.

Support was provided to a project aimed at increasing data on molecular epidemiology from eastern Europe and the Commonwealth of Independent States. In collaboration with the Instituto de Salud Carlos III in Madrid, the project has generated sequence data on HIV subtypes and CRFs driving the HIV epidemic in eastern Europe, which were published in peer reviewed journals⁴⁰ and presented at several major AIDS conferences. As part of this project, a training workshop was organized by the WHO Collaborating Centre in Madrid in November 2008 on methodology for molecular epidemiology studies, sequencing and phylogenetic analyses.

4.3.4 Design and analysis of clinical trials for malaria vaccines

With malaria vaccines progressing beyond proof-of-concept to pivotal phase III studies, standardization of methods and reporting practices in controlled trials of preventive interventions became a high priority. It was agreed that consensus-based guidance was needed for further WHO work on the analysis aspects of malaria vaccine field efficacy trials.⁴¹ Whereas most vaccine efficacy results are based on the first occurrence of the specified endpoint, children in many settings in Africa may experience several episodes of clinical malaria each year. Furthermore, the heterogeneity in risk is such that the rate of malaria disease varies substantially within many populations. Another complication is that the lead malaria vaccine candidate is thought to partially protect all vaccinees rather than completely protect some, earning it the title of a "leaky vaccine". Additional factors important for decision-making are the estimated duration of efficacy, an evaluation of severe malaria, malaria-related mortality and all-cause mortality and, if proven, protection against indirect morbidity.

Against this background, IVR published a systematic review on methods and reporting in paediatric randomized controlled trials of malaria preventive interventions⁴² and convened the 2008 meeting of the Malaria Vaccine Advisory Committee which provided consensus-based guidance on analysis of malaria vaccine efficacy.⁴³ The Committee also identified the need for targeted research to ensure that appropriate statistical methods are available to address the complexities in analysing malaria field efficacy data. IVR will publish this statistical research during 2010–2011 together with a guide to ensure field efficacy data are appropriately analysed and accurately communicated to policy-makers.

Within the INYVAX project, coordinated by the European Vaccine Initiative,* IVR is taking a lead role in a Brighton Collaboration working group for the harmonized

* The European Vaccine Initiative, European Economic Interest Grouping (EVI-EEIG), formerly the European Malaria Vaccine Initiative.

collection, analysis and reporting of safety data for malaria and tuberculosis vaccines, with an emphasis on developing country perspectives. Part of IVR's role is to guide the conduct of a systematic review of methods used for safety reporting in malaria and tuberculosis vaccine trials to date.

4.3.5 Standardization of malaria assays and reagents

The Malaria Vaccine Technology Roadmap highlighted the need for standardized assays and reagents to allow comparative evaluation of malaria vaccine development and enable efficient use of resources at the global level. Comparing the relative merits of different candidate vaccines and approaches in a credible and informed manner requires a baseline level of harmonization around the key assays that can be used for rational decision-making. Recent approaches have been undertaken by laboratories worldwide to work towards such standards.

As global coordinator in the EU-funded activity "OPTIMALVAC", IVR with the participation of PATH and MVI will facilitate the development of harmonized humoral and cellular immunoassays that can be applied during the development of new vaccines. This includes the conduct of proficiency panels comparing the outcome of the same assay at several centres, identifying factors to account for variability, and ultimately working towards a consensus standard operating procedure for each assay. Initial assays identified for harmonization are ELISpot and intracellular cytokine staining T-cell assays, antibody-dependent cellular inhibition assays and immunofluorescence assays for parasite protein recognition. Reference centres for the global malaria vaccine community are envisaged as a long-term outcome of this activity.

4.3.6 Tuberculosis assays

The joint IVR/Stop TB Task Force dealing with laboratory assays for use in TB vaccine clinical trials had developed a protocol for a widely implementable whole blood assay of interferon-gamma production following vaccination. It was recommended that the protocol be used to assure some comparability of the immunogenicity results of different vaccine candidates. It is encouraging that the assay protocol was implemented in all TB clinical trials initiated in 2008–2009 in Africa, Europe and the USA.

However, the value of the currently used immunological markers assessed in the laboratory assays is unclear, since none represents a true surrogate readout of clinical protection against TB disease. The Task Force therefore investigated the development of a functional test – a mycobactericidal assay – that could detect a causal link between vaccination and the killing of TB bacteria *in vitro*. Given that current mycobactericidal assays lack robust data on both inter- and intra-assay reproducibility, it was agreed that further studies were needed to provide a level of confidence that the assays are fit for purpose prior to incorporation in field trials.

To address this need, the Task Force organized two meetings in December 2007 and September 2008 to develop a plan to evaluate in head-to-head comparison several assays for their reproducibility and ease of use in field conditions. The study was initiated in mid 2009 with funding from the Aeras Global TB Vaccine Foundation and the conclusions are expected by the end of 2010.

4.3.7 Best practices for cost-effectiveness analyses

Cost-effectiveness tools aid decision-makers as they explore likely scenarios and optimal strategies for potential vaccine introduction, along with costs and benefits. Given the paucity of quality data, they also indicate the uncertainties and assumptions used in an analysis and contribute to transparency in the decision-making process. For example, although several systematic reviews of economic evaluations of pneumococcal and rotavirus vaccines exist, a structured and systematic comparison of the decision-making tools underlying the studies is lacking.

IVR therefore facilitated several workshops on systematic literature reviews and decision tool assessments to determine the cost-effectiveness of pneumococcal conjugate and rotavirus vaccines. The objective of the workshops was to guide country decision-makers on the strengths and potential pitfalls of existing mathematical models and cost-effectiveness tools available in both the public and private sectors. Participants learnt the importance of comparing different mathematical models to understand how they are structured, their attributes and key assumptions, and discussed the processes that lead to different results. Similarly, given the inherent complexity of this type of analysis, it is important to identify input parameters and assumptions that are critical drivers of the outcomes. Such a review can also inform surveillance needs and promote a more integrated approach to data gathering and analysis.

To improve the quality, transparency and comparability of economic evaluations, IVR published in 2008 practical guidelines⁴⁴ to assist economists and health service researchers in the public and private sectors to ensure relevant, reliable and consistent data for informed decisions.

4.4 Disease burden estimation

4.4.1 Assessment of mathematical models for measles

Mathematical models can aid programme planning and monitoring and the estimation of disease burden. Despite global progress in measles surveillance and reporting, accurate numbers of measles deaths are lacking for many countries, particularly those where the burden is highest. The Measles Strategic Planning tool to monitor progress towards measles goals was evaluated in 2008 by the IVR Advisory Committee on Quantitative Research in Immunization (QUIVER), which noted that the tool did not capture transmission dynamics or herd immunity. In 2009, an improved model to estimate the global burden of measles was presented to the Committee, and further refinements suggested, such as to vary the reporting fraction over time; to account for competing causes of death, and to validate models against

seroprevalence data in selected countries. The refined model was used to produce the measles mortality estimates in 2008 and to update the estimates from 2000–2007. In 2010, this next-generation model will be used to revise the time-series estimates of global measles mortality for 2000–2009, taking into account additional information on deaths in India.

4.4.2 Assessment of a cohort model to estimate pertussis burden

During the biennium, QUIVER assessed the US National Institutes of Health pertussis cohort model to produce WHO global estimates of the burden of pertussis cases and deaths, based on country estimates for children under and over five years old. Ad hoc working groups set up by SAGE and QUIVER assessed the structure of the model and its limitations, particularly in developing countries, and recommended refinements to include model validation and uncertainty analysis. An updated version is expected in 2010.

4.4.3 Assessment of models for neonatal tetanus

QUIVER assessed neonatal tetanus models developed by the London School of Hygiene and Tropical Medicine, United Kingdom to estimate neonatal deaths due to tetanus for 102 high mortality countries. The underlying principle of the model is that the proportion of children dying from neonatal tetanus depends on the proportion born without effective immunity; cord cutting at delivery; and cord care after delivery. These three factors might be estimated directly or from proxies. The first might be approximated from immunization data, the second from national data on skilled attendance at delivery (although this does not capture factors outside of “skilled” care), and the third, for which less data are available, could be estimated using female literacy as a proxy.

A random effects logistic regression model considered a number of covariates, including protection at birth coverage, skilled attendance rate, female literacy, region, time period, study design and case definition. Values were imputed where missing or implausible. QUIVER felt that the model approach seemed appropriate and that new (lower) estimates of neonatal tetanus mortality for the past were due to recently available data and the exclusion of China from the analysis. The observed biases in the model need further study.

4.4.4 Improving mathematical modelling: contact patterns in developing countries

Infectious diseases such as influenza-like illnesses can spread when individuals come into close contact with each other. More knowledge on these contact patterns will facilitate an understanding of transmission and help produce better predictive models of the spread of disease. This, in turn, will lead to improved estimates of the effectiveness and cost-effectiveness of alternative control programmes.

The social mixing for influenza-like-illness project was established by IVR to collect patterns that may be relevant to the spread of influenza in three south-east Asian

countries. The study protocol and instruments were developed in 2009 and a pilot study was carried out at a site in Viet Nam. In 2010, 2000 individuals will be sampled in Thailand and Viet Nam (1000 urban and 1000 rural), and in Indonesia 4000 individuals (2000 urban and 2000 rural) will be recruited into the study. The results of the study will be compared to similar data recently collected in two east Asian countries and in Europe. Estimation of *Who Acquires Infection from Whom* matrices will be made based on these social contact data. It is anticipated that a cadre of individuals with relevant experience could refine the estimates of contact patterns in south-east Asia and improve mathematical models of influenza spread in the region.

5

Performance and projections

5.1 Expected results 2008–2009

The WHO Medium Term Strategic Plan 2008–2013 is an integral element in WHO’s framework for results-based management and translates the long-term vision of the Organization into strategic objectives and measurable performance indicators. For 2008–2009, IVR set itself the following targets towards meeting the goals of WHO’s strategic objectives for communicable diseases.

KNOWLEDGE MANAGEMENT

Target	At least one consensus report is published on global research needs and priorities for vaccines or immunization technologies or strategies
Assessment	Achieved Human papillomavirus vaccines – WHO position paper. <i>Weekly Epidemiological Record</i> , 2009, 84(15):118–131
Target	Three consensus reports are published on global research needs, priorities and current status of HIV, tuberculosis or malaria vaccines and immunization strategies
Assessment	Achieved <ul style="list-style-type: none"> i) Report of a consultation on the optimization of clinical challenge trials for evaluation of candidate blood stage malaria vaccines. <i>Vaccine</i>, 2009, 27(42):5719–5725 ii) Report and position paper “AIDS vaccine for Asia network: expanding the regional role in developing AIDS vaccines” accepted for publication in <i>PLoS Medicine</i> iii) Second Geneva consensus: recommendations for novel live TB vaccines: report and recommendations from a meeting held at WHO HQ, April 2009 submitted to <i>Vaccine</i>
Additional target	Four developing country manufacturers are in the clinical development stages of producing influenza vaccine, through IVR support
Assessment	Achieved <ul style="list-style-type: none"> i) BioFarma completed clinical trials and registered its new seasonal influenza vaccine in Indonesia ii) Government Pharmaceutical Organization, Thailand initiated clinical trials in 2009 iii) Serum Institute of India initiated clinical trials in 2009 iv) Instituto Butantan Brazil is in advanced preparation of clinical trials

RESEARCH AND PRODUCT DEVELOPMENT

Target	At least one new or improved vaccine or immunization technology has received internationally recognized approval for use
Assessment	Achieved India approval for export of new meningitis A conjugate vaccine
Target	Three clinical trial endpoints and/or assays are developed and validated for clinical evaluation of vaccines for HIV, tuberculosis or malaria
Assessment	Surpassed i) MALVAC 2008: Measures of efficacy of malaria vaccines in phase 2b and phase 3 trials – scientific, regulatory and public health perspectives. <i>Vaccine</i> , 2009, 27(5):624–628 ii) Considerations regarding efficacy endpoints in HIV vaccine trials. <i>Vaccine</i> , 2009, 27(14):1989–1996 iii) Guidance on the evaluation of <i>Plasmodium vivax</i> vaccines in populations exposed to natural infection. <i>Vaccine</i> , 2009, 27(52):7228–7235 iv) Plan for comparative evaluation of mycobactericidal assays for reproducibility and appropriateness for field use: www.stoptb.org/wg/new_vaccines

IMPLEMENTATION RESEARCH

Target	The effectiveness of at least one new or improved immunization strategy or intervention has been determined and the evidence made available to appropriate institutions for policy decisions
Assessment	Achieved SAGE recommendations on the use of licensed human H5N1 influenza vaccines in the interpandemic period. <i>Weekly Epidemiological Record</i> , 2009, 84(24):244–248

As shown above, IVR was very successful in meeting the targets it had set itself at the beginning of the biennium. This was to a significant extent due to the sharing of expertise and resources among partners to achieve results. Since publication of the

Medium Term Strategic Plan in 2008, the strategic objectives and expected results of the Organization have been consolidated to facilitate the extensive collaboration required, and will be reflected in future targets and milestones. From 2010, WHO also expects to improve the alignment of resources to priority objectives.

5.2 IVR functions and operational performance indicators 2010–2011

The core functions of WHO are a framework for its strategic objectives at global, regional and country levels. They relate to leadership and partnerships; shaping the research agenda; norms and standards; ethical and evidence-based policies; technical support and building institutional capacity; and monitoring and assessment. These core functions are reflected in the IVR Strategic Plan 2010–2020² that will guide the work of the team over the next 10 years. Indeed, IVR's four strategic functions, with a particular focus on innovation, are:

- the identification of vaccine and vaccination research priorities;
- the development of research standards and guidelines;
- the strengthening of research and product development capacity; and
- the translation of research results into policy and practice.

Applying these strategic functions, IVR will focus on priority areas and lead projects that can have a significant impact on public health, particularly in developing countries. Monitoring and evaluation are, of course, an ongoing process to ensure the continued relevance of projects in the context of scientific developments, public health needs and the relative added value of IVR involvement. Selected key performance indicators per strategic function for 2010–2011 are provided below.

STRATEGIC FUNCTION	INDICATOR	OUTPUT 2008–2009	EXPECTED OUTPUT 2010–2011
Research priorities	Number of target product profiles developed through an IVR-managed process	1	1
Research standards	Number of regulatory standards developed based on IVR-sponsored research	1	2
Capacity strengthening	Number of developing country vaccine products licensed following technology transfer facilitated by IVR	2	3
Translation of research results	Number of SAGE policy recommendations informed by IVR-supported research	4	4

Notes

- ¹ World Health Organization, United Nations Children's Fund, World Bank. *State of the world's vaccines and immunization*, 3rd ed., Geneva, World Health Organization, 2009.
- ² IVR Strategic Plan 2010–2020: http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.02_eng.pdf.
- ³ WHO–UNAIDS Report: Public health considerations for the use of a first generation HIV vaccine, *AIDS*, 2003, 17:1–10.
- ⁴ Fourth meeting on influenza vaccines that induce broad spectrum and long-lasting immune responses, London, 9–10 November 2009: www.who.int/vaccine_research/diseases/influenza/meeting_09_10Nov09/en/index.html.
- ⁵ Clinical trials of pandemic influenza prototype vaccines: www.who.int/vaccine_research/diseases/influenza/flu_trials_tables/en/index.html.
- ⁶ WHO meeting on the role of neuraminidase in inducing protective immunity against influenza infection, Vilamoura, Portugal, September 14, 2008. *Vaccine*, 2009, 27:6366–6369.
- ⁷ WHO Virtual Consultation on the Safety of Adjuvanted Influenza Vaccines (3 June 2009): www.who.int/vaccine_research/InfluenzaMeeting/en/index.html.
- ⁸ Global pandemic influenza action plan to increase vaccine supply: progress report 2006–2008: http://whqlibdoc.who.int/hq/2009/WHO_IVB_09.05_eng.pdf.
- ⁹ Moorthy VS et al. Report of a Consultation on the Optimization of Clinical Challenge Trials for Evaluation of Candidate Blood Stage Malaria Vaccines, 18–19 March 2009, Bethesda, MD, USA. *Vaccine*, 2009, 27(42):5719–5725.
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- ¹⁵ Business plan for the global pandemic influenza action plan to increase vaccine supply: http://www.who.int/vaccine_research/documents/Report%20McKinsey%20Business%20Plan%20Flu3.pdf.
- ¹⁶ Pinder M et al. MALVAC 2009: Progress and challenges with development of whole organism malaria vaccines for endemic countries: http://www.who.int/vaccine_research/MALVAC_B/en/index.html (submitted to *Vaccine*).

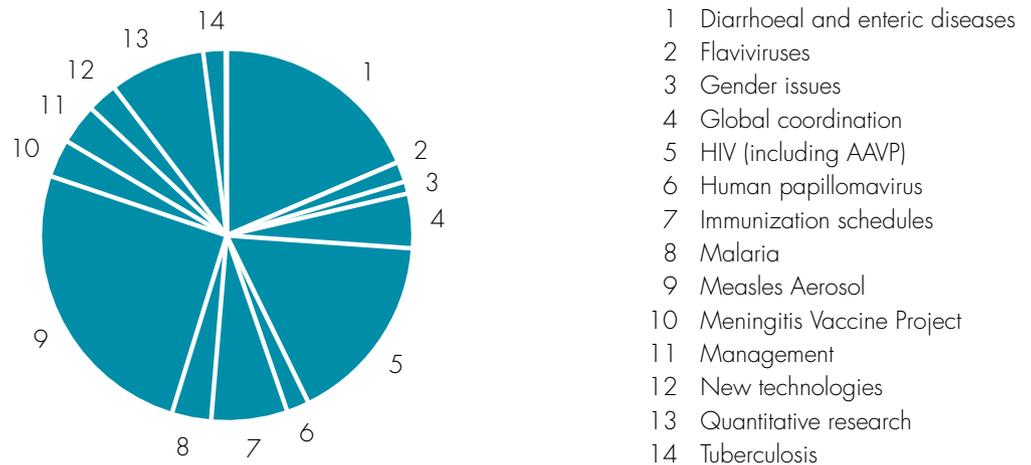
- 17 Mueller I et al. Guidance on the evaluation of *Plasmodium vivax* vaccines in populations exposed to natural infection. *Vaccine*, 2009, 27(41):5633–5643.
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- 27 Rotavirus vaccines. *Weekly Epidemiological Record*, 2007, 82(32):285–295.
- 28 Rotavirus vaccines: an update. *Weekly Epidemiological Record*, 2009, 84(51–52):533–537.
- 29 Human papillomavirus vaccines: WHO position paper. *Weekly Epidemiological Record*, 2009, 84(15):118–131.
- 30 For details of recent developments of the HPV Laboratory Network, see www.who.int/biologicals/areas/vaccines/hpv_labnet/en/index.html.
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- 35 Edelman R, Hombach J. Guidelines for the clinical evaluation of dengue vaccines in endemic areas: summary of a World Health Organization Technical Consultation. *Vaccine*, 2008, 26(33):4113–4119.
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- 37 Generic protocol for monitoring impact of rotavirus vaccination on gastroenteritis disease burden and viral strains: http://whqlibdoc.who.int/hq/2008/WHO_IVB_08.16_eng.pdf.
- 38 Considerations regarding efficacy endpoints in HIV vaccine trials. *Vaccine*, 2009, 27(14):1989–1996.
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- 44 Guide for standardization of economic evaluations of immunization programmes: http://whqlibdoc.who.int/hq/2008/WHO_IVB_08.14_eng.pdf.

Annex 1. IVR resources 2008–2009

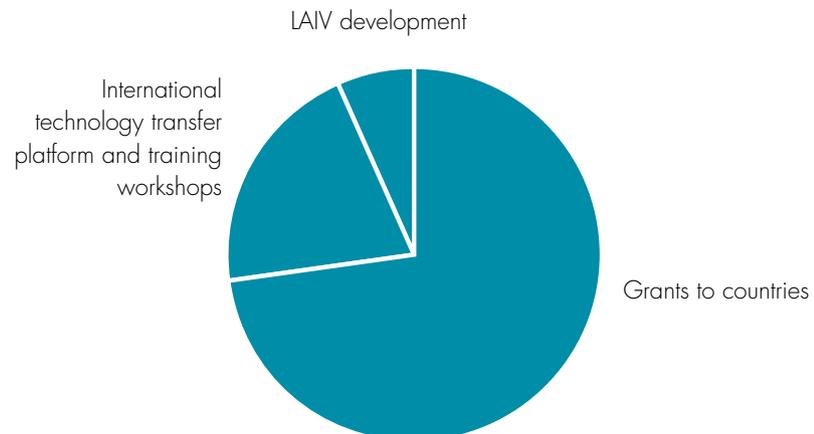
Total IVR/HQ project expenditure in 2008–2009 was US\$ 33 377 000. This figure does not include an approximate US\$ 7 500 000 salary costs, nor funds disbursed to other parts of WHO. In addition, it should be borne in mind that many projects with significant IVR involvement are carried out in partnerships with shared investment of human and financial resources, and are therefore not necessarily reflected in the charts below.

IVR EXPENDITURE BY ACTIVITY AREA, 2008–2009 (US\$ 11 493 000)¹



¹ without influenza technology transfer grants

PANDEMIC INFLUENZA ACTIVITY EXPENDITURE, 2008–2009 (US\$ 21 884 000)

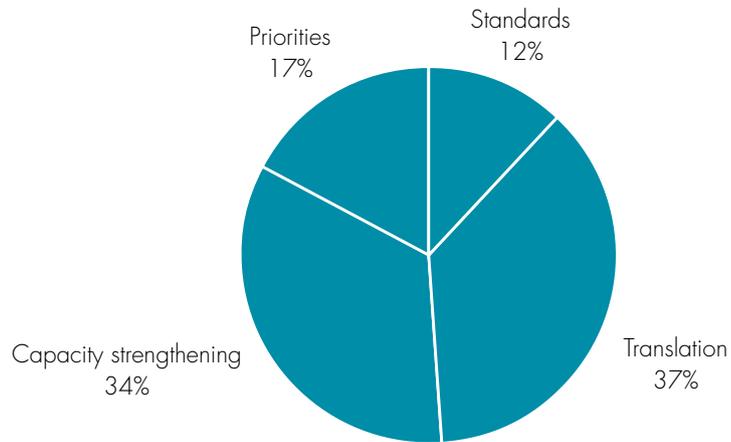


The IVR database of vaccine R&D projects allows a more detailed breakdown of IVR expenditures. In addition to a disease focus, the entries capture elements such as IVR's convening and coordination role, strengthening of developing country product development, regulatory and ethical capacities, intellectual property issues, and tools to guide policy-making.

Towards the end of the biennium 2008–2009, as part of a longer-term vision for vaccine development and vaccination research, IVR decided to approach its portfolio of projects and activities using the following four strategic functions that make up its mandate:

- i) identification of vaccine and vaccination research priorities;
- ii) development of research standards and guidelines;
- iii) strengthening of research and product development capacity; and
- iv) translation of research results into policy and practice.

Using these strategic functions, project expenditure during 2008–2009 included in the IVR database can be broken down as follows:



An estimated US\$ 20 million of grants to countries to build their capacity to produce influenza vaccine are not included in this chart. This ambitious project falls entirely under the strategic function of strengthening research and product development capacity.

Annex 2. IVR scientific journals 2008–2009

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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

After a decade of joint efforts, an affordable vaccine against group A meningococcus is now available. Five years from today, the vaccine should be protecting some 400 million people across African meningitis belt countries against deadly meningitis epidemics.

IVR-PATH Meningitis Vaccine Project



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