



WHO: working to ensure global  
**QUALITY, SAFETY AND STANDARDS**  
in immunization



**World Health  
Organization**

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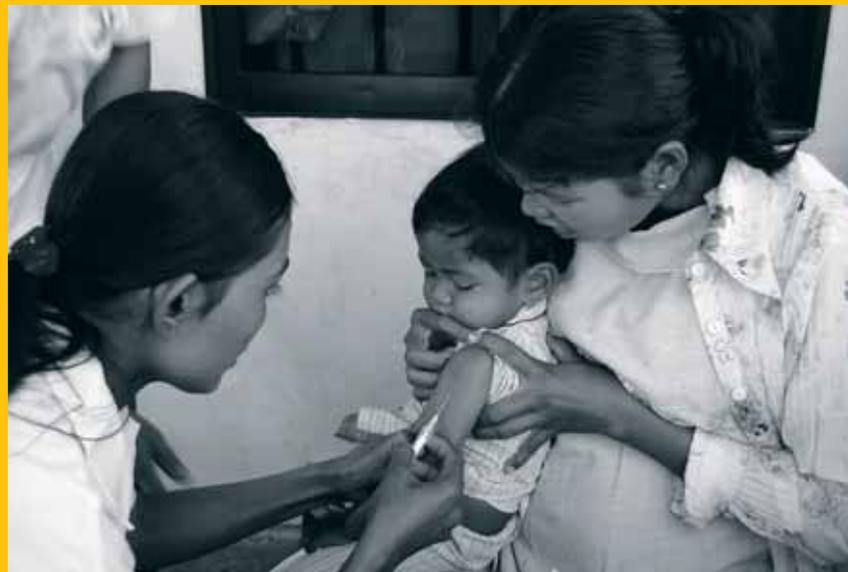
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# WHO'S QUALITY, SAFETY AND STANDARDS WORK IN IMMUNIZATION

A comprehensive approach to regulatory support



WHO's quality, safety and standards work in the area of immunization focuses on enabling the use of vaccines, other biological medicines and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards (both written and biological); ii) assuring the quality of vaccines and immunization equipment through both capacity strengthening of national regulatory authorities and prequalification activities; and iii) monitoring, assessing and responding to vaccine safety issues of global concern.



*A mother in Cambodia watches while her child is vaccinated*



## THE CHANGING VACCINE WORLD

Immunization is one of the most successful and cost-effective health interventions ever. Outstanding progress has been made towards polio eradication, measles mortality reduction and maternal and neonatal tetanus elimination. In addition, new vaccines against high burden vaccine-preventable diseases (such as *Haemophilus influenzae* type b, pneumococcal, rotavirus and human papillomavirus vaccines) are essential elements in meeting the Millennium Development Goals. Immunization also has an important role to play in controlling public health crises of global significance such as pandemic influenza.

## The challenges

**Global access to vaccines at affordable prices will, to an ever larger extent, rely on production in emerging economies such as Brazil and India, and vaccine-producing countries which have not previously supplied the global market. Human trials of new vaccines are increasingly being conducted in countries with the highest disease burden, which may not have experience in regulatory oversight of vaccine clinical trials. There are more vaccines in the research and development pipeline than ever before, some of which are primarily or only intended for developing countries.**

Such changes need to be accompanied by the development of regulatory capacity in developing countries such that they are able to ensure the safety, quality and efficacy of vaccines introduced in their countries.

Indeed, one of the guiding principles of the WHO/UNICEF Global Immunization Vision and Strategy (GIVS) for 2006-2015 is “assured quality and safe products and services”. GIVS aims to extend immunization services to those who are unvaccinated and to age groups beyond infancy, to introduce new vaccines and technologies, and to link immunization with the delivery of other health interventions.

WHO's Department of Immunization, Vaccines and Biologicals (IVB) has the overall aim of achieving a world in which all people at risk are protected against vaccine-preventable diseases. Assuring the quality and safety of vaccines and immunization is the mandate of the Department's Quality, Safety and Standards team, and is one of three fundamental components of the Department's work.





## SETTING NORMS AND STANDARDS

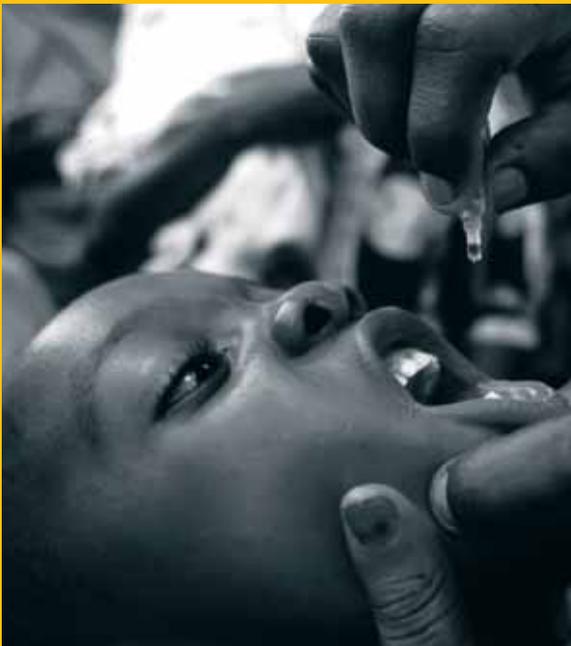
Established in 1947, the Expert Committee on Biological Standardization (ECBS) has overall responsibility for this area of work.

Standards developed through the ECBS relate to the production and quality control of safe and effective products. They provide guidance for national regulatory authorities and manufacturers and serve as the standard for acceptability of vaccines for supply to countries through international agencies (termed prequalification). Biological standards are also established by the Committee and provide the basis for the laboratory comparison of vaccines worldwide.

## Future focus

For the foreseeable future, the emphasis for work in this area will be on the development of standards for new vaccines and novel vaccine combinations and of strategies to promote, facilitate and monitor the use of WHO standards.

As expectations for faster product development of vaccines grow, the ECBS will need to develop guidelines at an earlier stage of the production cycle.



*Child receiving oral polio vaccine during a vaccination campaign in Sierra Leone*

## Rotavirus vaccines

Rotavirus is the leading cause of severe diarrhoeal disease and dehydration in infants and young children in both developed and developing countries and is estimated to kill approximately half a million children a year globally. Since 2005, two new rotavirus vaccines have been licensed and there is considerable interest in vaccine introduction projects and prequalified vaccines. At its 2005 meeting, the ECBS established WHO recommendations on the production and quality control of new rotavirus vaccines. The guidelines were subsequently presented to vaccine regulators in workshops aiming to promote and support the strengthening of regulatory capacity in developing countries for the evaluation of clinical trial proposals and data.

## Pandemic influenza vaccines

In 2005, the ECBS established new WHO guidelines on the safe production and quality control of human influenza vaccines produced in response to a pandemic threat. The existence of internationally agreed WHO specifications has enabled significant advances to be made in the development of prototype pandemic influenza vaccines.

## Accelerating regulatory approval for new polio vaccines

In 2004 and 2005, WHO coordinated support to accelerate the process of regulatory approval of two single-strain oral polio vaccines (mOPV1 and mOPV3), which are key tools in the final stages of polio eradication. In the spring of 2005, mOPV1 was made available for use in critical polio-endemic countries to stop transmission of the type 1 wild polio strain and to prevent outbreaks in non-endemic areas. mOPV3 was licensed in August 2005 and used for the first time in selected districts of India in December of the same year.



## ASSURING THE QUALITY OF VACCINES AND IMMUNIZATION EQUIPMENT

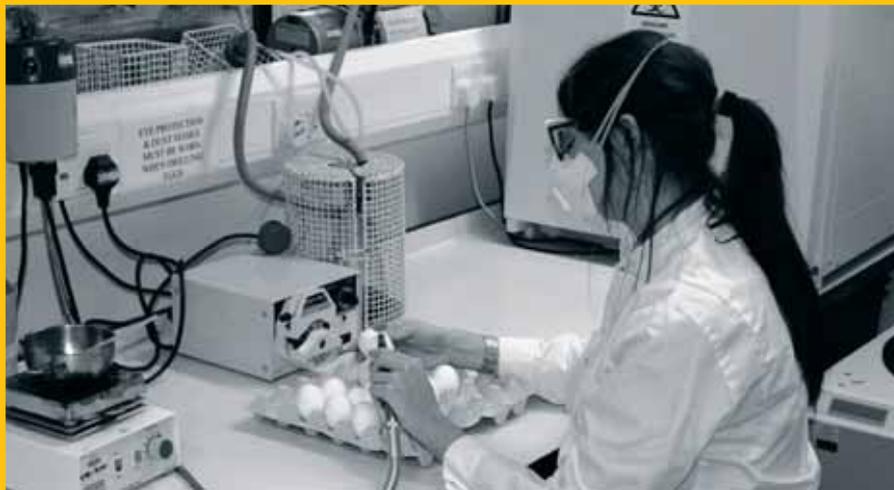
Through strengthening vaccine regulatory systems

The overall objective of a national regulatory authority for medical products is to ensure that all medicines, biologicals (including vaccines), and medical devices that are marketed in a country are of assured quality - assured by compliance with WHO standards - and are accompanied by appropriate information to promote their rational use.

Experience gained from national regulatory authorities worldwide indicates that many countries face challenges in developing an independent regulatory system and building capacity to implement effective regulation. In response to this challenge, WHO works with national regulatory authorities to identify their strengths and weaknesses, define priorities, and establish a development plan, which includes training and technical support. Strengths and areas to improve are determined using a WHO benchmarking system, whereby the regulatory authority is assessed for its fulfilment of a number of core regulatory functions. The functions that must be fulfilled depend upon the main source of the vaccines being used in the country. As at the end of 2006, 86 national regulatory authorities had been assessed by WHO. This represents 45% of WHO Member States and 70% of vaccine-producing countries.

In countries which produce vaccines, the national regulatory authority must have an independent system and exercise the following six regulatory functions: marketing authorization and licensing activities; post-marketing surveillance, including monitoring of adverse events following immunization; lot release; laboratory access; regulatory inspections of manufacturing sites and distribution channels; and authorization and monitoring of clinical trials.

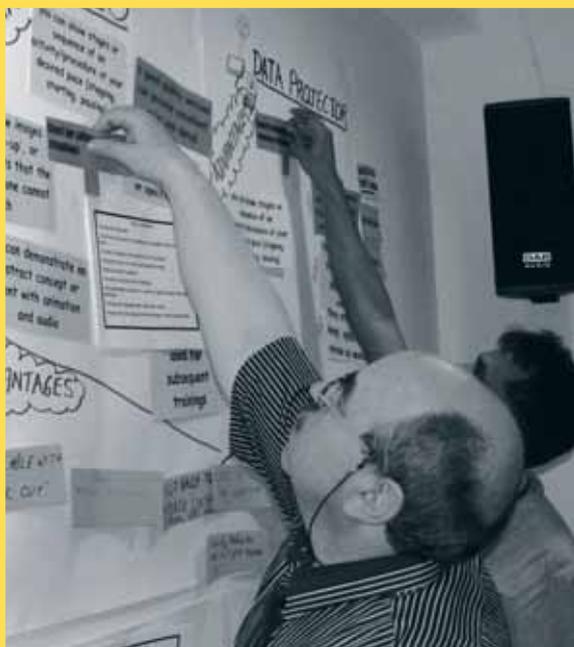
Successful implementation of WHO's work with national regulatory authorities through the above-mentioned approach has had a direct impact on ensuring the quality, safety and efficacy of regulated medical products in several countries.



*National regulatory authority assessments include laboratory access and regulatory inspections of manufacturing sites*

Ongoing WHO efforts to support countries targeted for clinical trials or licensing of new vaccines include:

- the establishment and facilitation of the Developing Country Vaccine Regulators Network;
- the organization of regulatory workshops;
- the establishment of/collaboration with regulatory support mechanisms, such as the African Vaccine Regulatory Forum, and the Association of Southeast Asia Nations "Vaccine Chapter", at the regional level;
- the development of regulatory procedures and training curricula for regulatory oversight of clinical trials; and
- ad hoc advice to individual countries requesting assistance.



*Participants considering vaccine quality issues at a Global Training Network workshop*

Another area of activity which is key to the strengthening of regulatory capacity at country level is training. The Global Training Network on Vaccine Quality, established in 1996, provides support to staff of national regulatory authorities, national control laboratories, public sector manufacturers and national immunization programmes in the areas of vaccine regulation, surveillance of adverse events following immunization and vaccine quality.

### Developing Country Vaccine Regulators Network

Since its establishment in September 2004, the Developing Country Vaccine Regulators Network has met twice a year to discuss regulatory issues relevant to the clinical evaluation of vaccines to protect against tuberculosis, human papillomavirus, HIV, rotavirus, typhoid, Japanese encephalitis and dengue. These meetings provide the opportunity for exchange of information among regulators of developing countries as well as between regulators in countries where vaccines are developed and/or manufactured and regulators in countries targeted for clinical trials and/or vaccine introduction. The Network has also developed a training course on inspections of clinical trials and is in the process of establishing "centres of excellence" in Africa and Asia, which will serve as regional hubs for regulatory support.

### Global Training Network on Vaccine Quality

The Global Training Network on Vaccine Quality includes courses delivered at global, regional and country level. Although courses generally follow standardized curricula, they can also be tailor-made such that they meet specific country needs in the different regulatory functions. As new needs for training are identified through the various activities supporting regional or national regulatory mechanisms, new curricula for incorporation into these courses are developed.

## Through prequalification activities

WHO has, for many years, evaluated vaccines to assess their suitability for provision to countries through international agencies. This process is called prequalification. Prequalification is only possible for vaccines produced in countries where the national regulatory authority effectively exercises all required oversight responsibilities, as verified by WHO. The manufacturer submits a product summary file detailing production methods, vaccine composition, and quality controls. Consecutive lots of vaccines are independently tested by laboratories qualified by WHO, and WHO experts conduct site visits to ensure that vaccines and production methods conform to international standards. Random testing and regular reassessment procedures ensure the continued quality of the product. The supply of vaccines through this system enables countries without a functional national regulatory authority to be supplied with vaccines of assured quality.

Countries using prequalified vaccines must license these vaccines before they can be used in the country. In order to accelerate vaccine introduction in such countries, WHO is developing guidelines to enable them to license such vaccines more rapidly, efficiently and effectively than has been the case in the past.

Prequalification activities at WHO have greatly increased since the establishment of the system. During the period 1986-2006, the number of types of vaccines to be prequalified increased fourfold, from six to 24. The number of manufacturers to have a vaccine prequalified increased from 13 to 22 over the same period. Interestingly, the percentage of manufacturers with prequalified vaccines based in emerging economies increased from 13 to 55 over the period.

With regard to the prequalification of immunization equipment, a similar process to that in place for vaccines was established for injection devices in 2005. The system, termed the Performance, Quality and Safety system, places increased emphasis on application of international standards and quality assurance in the manufacturing process, and also takes into consideration feedback from users in the field. The same process is being established for other types of immunization equipment (cold and freezer rooms, refrigerators, cold boxes, vaccine carriers, temperature monitoring devices and waste management equipment).

## Future focus

It is likely that the adequate supply of vaccines required by developing countries in the future will largely be dependent on the regulatory capacities of national regulatory authorities in developing countries. Priority will be given to facilitating capacity-building in these countries.

As demands on the WHO prequalification procedure increase, focus will be on expanding staff capacity such that the efficiency of the process is increased.

As new areas of the Performance, Quality and Safety system are developed, the focus will be on both the prequalification of currently registered equipment, and different types of equipment, such that potential purchasers are presented with an increased choice of products.

The future emphases of the Global Training Network on Vaccine Quality will be: 1) to develop new courses relating to the regulation of new vaccines coming onto the market; 2) to establish an accreditation system for training centres; and 3) to introduce adult learning methodologies to course curricula.





## MONITORING, ASSESSING AND RESPONDING TO VACCINE SAFETY ISSUES OF GLOBAL CONCERN

Once vaccines are licensed for general use and are administered to large populations, monitoring continues to identify uncommon adverse events following immunization, events that may occur after a long time, or events that may occur in specific subgroups of the target population.

Typically, monitoring of licensed vaccines is done through spontaneous reporting systems whereby adverse events that follow immunization are reported to health authorities. Sometimes such post-marketing surveillance is conducted in more formal Phase IV clinical trials.

Many developing countries are faced with the challenge of not having a post-marketing surveillance system, while for many that do, strengthening the system to be able to more effectively monitor safety remains an ongoing challenge. Globally, the need to strengthen monitoring is more critical when vaccines being introduced in developing countries are not being used concomitantly in developed countries with more effective monitoring systems. For some vaccines there is also a need to understand their safety profile when introduced in developing countries in the context of different immunization schedules and different background population characteristics. WHO's Quality, Safety and Standards team is developing initiatives, in collaboration with other partners in vaccine pharmacovigilance, to ensure a high standard in the collection, analysis and interpretation of vaccine safety data at the global level.

These initiatives aim to:

- strengthen routine surveillance systems in individual countries;
- standardize post-marketing activities across countries (including through special networks for selected issues such as the establishment of the safety profile of new vaccines and the safety of pandemic influenza vaccines);
- improve access to data collected by individual countries through submission to the WHO Programme for International Drug Monitoring;
- improve development and use of vaccine-specific terminologies and analysis tools; and
- increase investigation of specific safety issues through epidemiological research approaches.

### New network for vaccine safety monitoring

WHO has initiated the establishment of a network of countries in the developing world which already have strong post-marketing surveillance systems, to monitor the safety of new vaccines as they are introduced. The network, currently in its introductory phase, will focus on post-marketing surveillance for vaccines supplied through United Nations agencies. It is expected, however, that its activities will, in due course, be extended to other vaccines. The network will also be part of overall efforts to increase analytical capacity for vaccine safety data and to detect potential signals of serious adverse events for further investigation.



## Global Advisory Committee on Vaccine Safety

WHO's Global Advisory Committee on Vaccine Safety considers vaccine safety issues of potential global importance. Created in 1999, the Committee reviews, at its biannual meetings, the latest knowledge on vaccines, in close collaboration with experts from national governments, academia, and industry. It assesses the evidence for relationships between vaccines and/or their components, and adverse events attributed to them. It creates, where necessary, ad hoc task forces to commission, monitor and evaluate related research. Examples of topics reviewed by the Committee include the safety of thiomersal; hepatitis B vaccination and multiple sclerosis; measles, mumps and rubella (MMR) vaccination and autism; and safety issues associated with seasonal and pandemic influenza vaccines.



Home page of the Global Advisory Committee on Vaccine Safety web site

## Global Advisory Committee on Vaccine Safety

The Global Advisory Committee on Vaccine Safety publishes its conclusions and recommendations in the WHO Weekly Epidemiological Record. Recommendations and conclusions, together with additional information, are posted in Arabic, Chinese, English, French, Russian and Spanish on the Committee's web site [http://www.who.int/vaccine\\_safety/en/](http://www.who.int/vaccine_safety/en/).

## Vaccine Safety Net

Paradoxically, as immunization programmes become more successful and the diseases which they prevent less widespread, some of these diseases are no longer perceived as a threat, leading certain groups to question the utility of vaccination. In recent years, the number of web sites providing unbalanced, misleading and alarming vaccine safety information has increased, making it difficult to identify and access reliable sources of information on the web.

Acknowledging the above-mentioned issues and urged by governments, key non-governmental organizations and UNICEF, WHO initiated, in 2003, the Vaccine Safety Net Project. Through this Project, which aims to facilitate the access of public health authorities, health professionals and the public to reliable information on vaccine safety, web sites are evaluated for their adherence to criteria, established by the Global Advisory Committee on Vaccine Safety, for good information practices for vaccine safety web sites.

Those complying with the credibility and content criteria defined by the Committee are listed on the Vaccine Safety Net pages of the WHO web site [http://www.who.int/immunization\\_safety/safety\\_quality/vaccine\\_safety\\_websites/en/](http://www.who.int/immunization_safety/safety_quality/vaccine_safety_websites/en/). The organizations with compliant sites are encouraged to create links on their web sites to other sites within the network.



*Togolese child with vaccination card after being vaccinated against measles*

## Future focus

The Global Advisory Committee on Vaccine Safety now systematically reviews safety issues potentially associated with vaccines recently introduced or under development. This helps provide direction to national regulatory authorities for the monitoring of clinical trials and dealing with requests for licensure. This new focus by the Committee will be especially important in the coming years as many new vaccines being introduced in developing countries will include novel vaccine concepts and components or new routes of administration and developing countries often have limited regulatory capacity.

In addition, the Committee is becoming actively involved in improving the processes for ensuring that appropriate information pertaining to adverse events following immunization reaches the global level for analysis.

With regard to post-marketing surveillance, particular emphasis will be placed on expanding and consolidating the network of developing countries to monitor the safety of newly-introduced vaccines. Collaboration with other international immunization initiatives and drug pharmacovigilance programmes will be increased in order to further strengthen global vaccine safety monitoring.

The future focus of the Vaccine Safety Net Project will be further expansion of the network to web sites in languages other than English and to web sites from all regions of the world.

# FUNDING

WHO's ability to successfully implement all activities mentioned in this document is dependent on sufficient human and financial resources at both global and regional levels.

The total income required for quality, safety and standards work globally in 2008-9 is US\$ 37 million, or nearly US\$ 20 million per year. Main sources of income for this period are UNICEF, the Bill & Melinda Gates Foundation, Australia, fees related to prequalification, and WHO core resources.

There is expected to be a significant shortfall for this same period. Although a number of promising fundraising initiatives are ongoing to address this gap, potential new funds fall far short of needed funds. In the event that this gap is not filled, WHO's ability to respond to

the need for global standards for new vaccines, or to update global standards for existing vaccines, will be affected. This will have implications for the activities described in this publication, for management of the WHO prequalification programme and the strengthening of national regulatory authorities. Ultimately new vaccine introduction and access to safe and effective vaccines of assured quality at country level will be negatively affected. Investments made by the GAVI Alliance and other stakeholders in the immunization world will be compromised.



# INFORMATION SOURCES

## Web sites

Immunization standards

[http://www.who.int/immunization\\_standards/en/](http://www.who.int/immunization_standards/en/)

Biologicals

<http://www.who.int/biologicals/en/>

Vaccine prequalification

[http://www.who.int/immunization\\_standards/vaccine\\_quality/vq\\_index/en/](http://www.who.int/immunization_standards/vaccine_quality/vq_index/en/)

Performance, Quality and Safety

[http://www.who.int/immunization\\_standards/vaccine\\_quality/pqs/en/](http://www.who.int/immunization_standards/vaccine_quality/pqs/en/)

Global Training Network on Vaccine Quality

[http://www.who.int/immunization\\_standards/vaccine\\_quality/gtn\\_index/en/](http://www.who.int/immunization_standards/vaccine_quality/gtn_index/en/)

Immunization safety

[http://www.who.int/immunization\\_safety/en/](http://www.who.int/immunization_safety/en/)

Global Advisory Committee on Vaccine Safety

[http://www.who.int/vaccine\\_safety/en/](http://www.who.int/vaccine_safety/en/)

Global Immunization Vision and Strategy

<http://www.who.int/immunization/givs/en/>

Immunization, Vaccines and Biologicals

<http://www.who.int/immunization/en/>

## Press materials

The safety of immunization delivery improves over last five years, but challenges remain (November 2005)

<http://www.who.int/mediacentre/news/releases/2005/pr59/en/>

Web sites providing information on vaccine safety recognized for complying with good information practices (May 2005)

[http://www.who.int/immunization/newsroom/NP\\_websites\\_10\\_05\\_2005.pdf](http://www.who.int/immunization/newsroom/NP_websites_10_05_2005.pdf)

First international standard for common genetic test approved by WHO (November 2004)

<http://www.who.int/mediacentre/news/releases/2004/pr84/en/>

## Fact sheet

Quality and safety of vaccines from development to delivery (November 2005)

<http://www.who.int/mediacentre/factsheets/fs295/en/>

## Meeting reports

Expert Committee on Biological Standardization

[http://www.who.int/biologicals/expert\\_committee/en/](http://www.who.int/biologicals/expert_committee/en/)

Global Advisory Committee on Vaccine Safety

[http://www.who.int/vaccine\\_safety/reports/en/](http://www.who.int/vaccine_safety/reports/en/)

WHO Steering Committee on Immunization Safety

[http://www.who.int/immunization\\_safety/ispp/ispp\\_final\\_report\\_Steering\\_Committee/en/index1.html](http://www.who.int/immunization_safety/ispp/ispp_final_report_Steering_Committee/en/index1.html)



## Immunization, Vaccines and Biologicals Department | Main functions and structure

### Director's Office



#### Immunization policy

- Strategic Advisory Group of Experts
- Other advisory committees
- Publications, Document Centre, web site

#### Management/External Relations

- Resource management
- Coordination with regions
- Advocacy and communication

Led by Dr Jean-Marie Okwo-Bele, the Director's Office is in charge of immunization programme policy, planning and coordination. It also carries out communication, advocacy and media relations, in addition to resource mobilization and management of funds.

### Innovation

#### Initiative for Vaccine Research

- Implementation research
- Product research
- HIV Vaccine Initiative
- Research on influenza vaccines

Focuses on accelerated discovery, development, evaluation and support for early introduction of new vaccines, other biological products, immunization technologies and strategies. This includes the development of pandemic influenza vaccines. IVR is composed of three teams which concentrate on: 1. product research and development; 2. implementation research; and 3. HIV, tuberculosis and malaria vaccines.



*This Initiative is led by Dr Marie-Paule Kiény.*

### Quality & Safety

#### Quality, Safety and Standards

- Norms and standards
- Vaccine quality
- Global safety issues

Focuses on defining and promoting international norms and standards of quality and safety for vaccines, other biological medicines, and immunization-related equipment. Activities cover: 1. setting norms and standards (both written and biological); 2. ensuring use of quality vaccines and immunization equipment through prequalification activities and capacity strengthening of national regulatory authorities; and 3. monitoring, assessing and responding to immunization safety issues of global concern.



*This team is led by Dr David Wood.*

### Access

#### Expanded Programme on Immunization

- Immunization systems strengthening
- Accelerated disease control
- Introduction of new and underutilized vaccines
- Vaccine supply and immunization financing
- Strategic information

Focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: 1. immunization systems strengthening, including expansion of immunization services beyond the infant age group; 2. accelerated control of measles and maternal and neonatal tetanus; 3. introduction of new and underutilized vaccines; 4. vaccine supply and immunization financing; and 5. disease surveillance and immunization coverage monitoring for tracking global progress.



*This team is led by Dr Thomas Cherian.*

Staff working in the Quality, Safety and Standards team





**QUALITY, SAFETY AND STANDARDS**  
the foundation of effective immunization