A Culture of Prevention:

A Model for Control of Vaccine-preventable Diseases

XVI Meeting of the Technical Advisory Group on Vaccine-preventable Diseases
Mexico City - November 3-5, 2004

Final Report

Pan American Health Organization

Regional Office of the World Health Organization

Table of Contents

Members of the XVI Technical Advisory Group on Vaccine-preventable Diseases

Dr. Steve Cochi
Acting Director, National Immunization Program
Centers for Disease Control and Prevention, Atlanta, Georgia, United States

Dr. J. Peter Figueroa **Rapporteur**
Chief, Epidemiology and AIDS
Ministry of Health, Kingston, Jamaica

Dr. Akira Homma
Director, Bio-Manguinhos/Fiocruz, Rio de Janeiro, Brazil

Dr. John R. La Montagne
Deputy Director, National Institute of Allergy and Infectious Diseases
National Institutes of Health, Bethesda, Maryland, United States

Dr. Joseph Z. Losos
Senior Scientist, Public Policy, Institute for Population Health
University of Ottawa, Ontario, Canada

Dr. Fernando Muñoz Porras
Ministry of Health, Santiago, Chile

Dr. Ciro A. de Quadros **Chairman**
Director, International Programs
Sabin Vaccine Institute, Washington, D.C., United States

Dr. Roberto Tapia-Conyer
Under-Secretary, Disease Prevention and Control
Ministry of Health, Mexico, D.F., Mexico

Dr. Jon K. Andrus **Ad-hoc**
Chief, Immunization Unit **Secretary**
Pan American Health Organization, Washington, D.C., United States

Dr. Donald A. Henderson **Member**
Professor of Medicine and Public Health, University of Pittsburgh **Emeritus**
Resident Scholar, Center for Biosecurity, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, United States Johns Hopkins University Distinguished Service Professor and Dean Emeritus, Johns Hopkins School of Public Health, Baltimore, Maryland, United States

Introduction

The XVI Meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases of the Pan American Health Organization (PAHO) was held from 3 to 5 November in Mexico City, Mexico. The TAG reviewed the current status of immunization programs in the Region of the Americas, implications of the worldwide immunization efforts, and the challenges ahead. It also made recommendations on how to accelerate the rubella and Congenital Rubella Syndrome (CRS) elimination initiative, while maintaining achievements and strengthening immunization programs.

The meeting was opened with a video message from Dr. Mirta Roses Periago, Director of the Pan American Health Organization. In welcoming the participants, Dr. Roses emphasized the strong support from PAHO to immunization initiatives and expressed her hope that the TAG would provide technical guidance on how to best take this strong program to a new level of achievement. Dr. Peter Figueroa, Chief, Epidemiology and AIDS, Ministry of Health, Jamaica, served as Chairman of the meeting, with Dr. Steve Cochi, Acting Director, National Immunization Program, Centers for Disease Control and Prevention, USA, as Rapporteur. Dr. Jon K. Andrus, Chief, Immunization Unit served as ad-hoc Secretary on PAHO's behalf. Long-standing Chairman of TAG, Dr. D.A. Henderson retired from this position and passed the chairmanship to Dr. Ciro de Quadros, Director, International Programs, Sabin Vaccine Institute, who was unable to attend the meeting. Both PAHO and the Mexican National Academy of Medicine formally recognized Dr. Henderson for his contribution.

TAG member, Dr. John La Montagne, Deputy Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA, died in the Mexico City airport upon arrival Tuesday night, 2 November 2004. The TAG and other meeting participants noted his tremendous contribution to public health.

PAHO invited to the meeting representatives from 10 states of Mexico, the host country, who received recognition for their excellent performance under the National Incentive Program, "Caminando a la Excelencia". TAG recognizes this practice as an effective way to motivate health personnel. Also present were the Ministers of Health of El Salvador and Peru, and the Vice-Ministers of Health of Bolivia and Paraguay. The PAHO Award for Immunization was presented to the immunization programs of El Salvador and Ecuador. The Minister of Health of El Salvador and the EPI Manager of Ecuador accepted the award on behalf of their national programs. The award is presented to the programs, persons, or institutions who have made outstanding contributions to immunization programs in the Region.

This report summarizes the technical deliberations of the XVI TAG Meeting and contains the main TAG recommendations. Since the last TAG meeting, held in Washington, D.C. in November 2002, the immunization programs of the Region of the Americas have maintained the continent free of indigenous wild poliovirus transmission, have interrupted endemic transmission of indigenous measles virus, and have made great

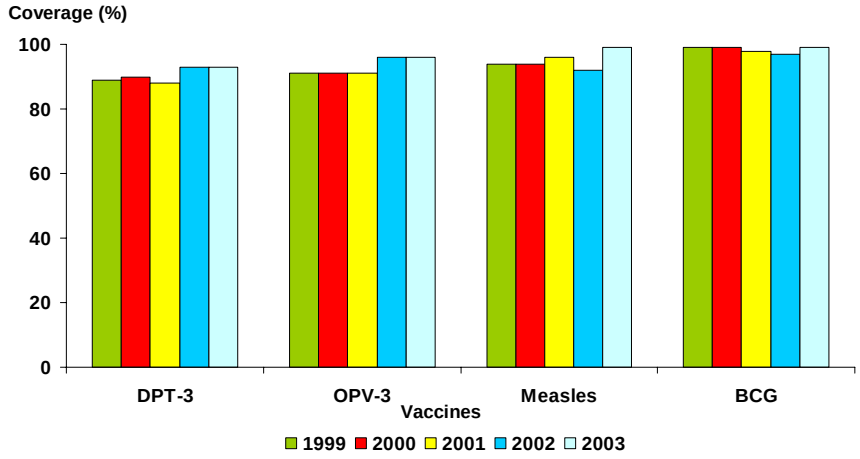
strides toward the goal of eliminating rubella and CRS by starting mass vaccination campaigns in adults and implementing rubella/CRS Plans of Action. Over the years, vaccination has saved millions of children and has contributed to a decrease in childhood mortality in the Americas; for the period 1990-1995, there were 51.4 deaths per 1,000 live births, and by 2003 the mortality rate had dropped to 30.7. Millions of children have also been spared serious illness and thousands of birth defects have been prevented. Regional coverage remains above 90% for all antigens. In 2003 and 2004, the whole Region conducted an annual Vaccination Week with the main objective to reach children and mothers who are not typically served by immunization services. Immunization programs are now positioning themselves to contribute to the end game of polio eradication, to maintain the success of measles elimination, to eliminate rubella and CRS, and to help countries determine the best ways to introduce new vaccines.

The TAG would like to acknowledge the remarkable progress achieved by PAHO's Immunization Unit (IM) over the last two years in coordinating technical support to Member States. Activities have included advancing the Directing Council Resolution CD44.R1 in September 2003 for rubella and CRS elimination, organizing two ad-hoc expert group meetings on rubella and measles, convening a regional rotavirus meeting in Peru and a global rotavirus meeting in Mexico City, assisting in the development of regional and country Plans of Action, conducting three country evaluations, organizing and supporting the Vaccination Week in the Americas, and advising on numerous country-based surveillance activities. Despite this progress, the TAG is concerned that IM lacks sufficient administrative and technical staff, especially in light of the record expenditures realized this year by the PAHO Revolving Fund for Vaccine Procurement and the technical challenges the Unit faces in providing countries with adequate assistance for strengthening surveillance and introducing new vaccines.

Routine Immunization

In spite of social, political and financial challenges, routine immunization coverage at the regional level remains above 90% for all vaccines (Figure 1).

Figure 1. Immunization coverage in children aged 1 year Region of the Americas *, 1999-2003

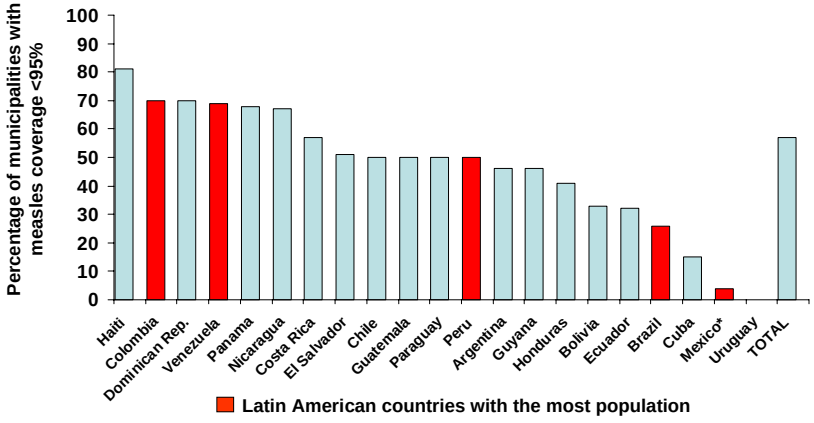


*** Does not include United States and Canada**

Source: Country Reports

While national coverage is high throughout the Region, a significant proportion of municipalities still have coverage <95% (Figure 2). This inequity is more pronounced in certain countries. National immunization programs and PAHO support should focus on increasing resources and developing strategies to overcome these low rates.

Figure 2. Percentage of municipalities with measles coverage <95% in children aged 1 year, Latin America, 2003



*** Coverage data <90% as reported in the WHO/UNICEF Joint Reporting Forms**

Source: Country reports for EPI Indicator Tables.

There is now consensus on the role played by the health sector: to ensure sustainable economic growth and poverty reduction by way of securing access to essential health services. This provides a unique opportunity to maintain and expand the reach of immunization programs in the Americas. Within this context, the activities of immunization programs are key public health interventions. Coverage and surveillance data should be used at the national level to measure performance of primary health care teams and local sanitary authorities. The TAG recognizes the significant impact that EPI will have on achieving the Millennium Development Goals in the countries of the Americas.

Rubella

In September 2003, PAHO's 44th Directing Council adopted a resolution to eliminate rubella and CRS by 2010 and urged Member States to prepare national Plans of Action in support of that objective. The elimination of rubella and CRS in the Americas has been defined as the successful interruption of endemic transmission of rubella virus in all countries of the Region without the occurrence of CRS cases associated with endemic transmission.

As of July 2004, approximately 99% of new birth cohorts in the Region of the Americas have had access to the combination measles, mumps and rubella vaccine (MMR). Only Haiti has yet to include the rubella antigen in its vaccination schedule. In 2002, all countries of the Region began conducting follow-up campaigns (second immunization opportunity for children aged <5 years) using the measles-rubella vaccine (MR), achieving >90% coverage. Between 1998 and July 2004, the English-speaking Caribbean, Costa Rica, Honduras, El Salvador, Mexico and Ecuador conducted adult vaccination campaigns targeting women and men. Campaigns in Brazil and Chile targeted only women of childbearing age (WBCA). During the campaign, coverage in the Caribbean reached 80%, while the other countries achieved coverage rates >95%. The remaining countries in the Region plan to conduct adult vaccination campaigns between 2005 and 2007.

Particular challenges of conducting adult vaccination campaigns included monitoring of vaccine safety and ensuring safe immunization practices. Also, since persons cannot donate blood for one month following rubella vaccination, campaigns had to be coordinated with blood banks to avoid shortages in blood supply. Since the introduction of the vaccine and launch of vaccination campaigns, rubella incidence has fallen 99.3% - from 135,000 reported cases in 1998 to only 923 in 2003. In 2004, five of the six indicators for integrated rubella/measles surveillance were >80% at the regional level.

While only 18 countries/territories in the Americas reported on CRS in 1998, by 2003 the entire Region was conducting CRS surveillance. In total, 44 cases were reported in 1998, 63 in 1999, 90 in 2000, 41 in 2001, 24 in 2002, and 14 in 2003. However, a continued effort to strengthen CRS surveillance is needed.

Argentina, Brazil, Costa Rica, El Salvador, and Peru conducted retrospective studies in obstetrics hospitals and in schools for the deaf and blind to identify children with probable or confirmed CRS. The implementation of high-quality CRS surveillance (periodic well-baby check-ups or setting up special clinics for consultations for congenital infections) is essential to strengthen health care services in the detection of congenital conditions and comprehensive perinatal care. Sensitive surveillance will improve clinical follow-up and case management of affected children.

According to a 2004 estimate, the cost of eliminating rubella and CRS in the Americas by 2010 is US$181 million. Of this, approximately $35 million (20%) would

be expected to come from PAHO/WHO regular funds and donors, and the remaining US$146 million (80%) from the countries. The considerable savings and benefits achieved by eliminating CRS far exceed the costs.

TAG commends members of the Regional Inter-Agency Coordinating Committee (ICC) for their efforts in strengthening the partnership towards the goal of rubella/CRS elimination in the Americas.

Recommendations:

Surveillance

In 1994, a regional measles eradication surveillance system was developed. This active system targeted the establishment of at least one reporting site per district. Since 1996, suspected measles cases that were IgM negative for measles have been tested for rubella IgM antibodies. In 1999, this active system was expanded into a measles-rubella integrated surveillance system to allow for simultaneous laboratory analysis. The objectives of the rubella component of the integrated surveillance system are to determine where the virus is circulating, to detect rubella cases in a timely manner in order to implement outbreak control measures, and to determine the impact of interventions.

1. The TAG endorses the rubella/CRS definitions based on the deliberations of the Meeting of the Ad-hoc Panel of Experts in Rubella and Measles held in Washington, D.C. in March 2004, cited in PAHO's EPI Newsletter of April 2004 (EPI Newsletter: *Meeting of Ad-Hoc Panel of Experts in Rubella and Measles.* April 2004, Vol. XXVI (2), <http://www.paho.org/English/AD/FCH/IM/sne2602.pdf>). (Annex 1). The definitions cited in the measles section also apply in full to rubella elimination.

2. For elimination purposes, full integration of measles and rubella surveillance is required; integrated laboratories are an important aspect of this surveillance system. Emphasis must be on active surveillance. Except in an outbreak setting, all specimens must be tested for both measles and rubella.

    - The TAG endorses the indicators currently reported in the PAHO Measles/Rubella Bulletin, with the revisions suggested by the Ad-Hoc Panel of Experts in Rubella and Measles (EPI Newsletter: *Meeting of Ad-Hoc Panel of Experts in Rubella and Measles.* April 2004, Vol. XXVI, (2), <http://www.paho.org/English/AD/FCH/IM/sne2602.pdf>). (Annex 1). Three indicators are particularly critical: the proportion of suspected cases with an adequate investigation, the proportion of suspected cases with an adequate blood sample, and the proportion of transmission chains with representative samples for virus isolation.

- An adequate case investigation includes a home visit within 48 hours of notification, completeness of relevant data (i.e., date of notification, date of investigation, date of rash onset, date sample taken, type of rash, presence of fever, dates of previous measles/rubella vaccinations), and active case searches.

- Efforts should continue to monitor reported measles/rubella cases by age, sex, location, and vaccination status.

3. In the context of CRS elimination, high-quality surveillance requires an active component and a sensitive case definition. The TAG recommends the following definition to guarantee rapid investigation of suspected CRS cases:

   - Suspected CRS case - A health care worker at any level of the health care system should suspect CRS in an infant when: (1) one or more of the following birth outcomes are detected: congenital cataracts, congenital cardiac defects, purpura or deafness; or (2) An infant's mother was known to have had laboratory-confirmed or suspected rubella infection during pregnancy. For diagnosis, a more specific definition may be appropriate, with laboratory confirmation remaining the gold standard.

   - During elimination, all suspected CRS cases should have specimens collected for IgM testing and virus isolation.

4. The TAG recommends that PAHO convene an ad-hoc meeting of experts to determine lessons learned and define good public health practice for establishing CRS surveillance. Issues to consider include review of existing literature and country experience, as well as reaching out to tap the expertise of professionals in various fields who come into contact with CRS-affected children. This includes, but is not limited to, ophthalmologists, cardiac surgeons, schools for the deaf, otorhinolaryngologists, and pediatric infectious disease specialists. This meeting should help to refine surveillance approaches and case detection strategies, for instance the use of low-birth weight as an investigation trigger to narrow the scope of perinatal screening.

5. Collaboration with the regional Perinatology Information System of the Latin American Center for Perinatology and Human Development (CLAP) and the Latin American Collaborative Study of Congenital Malformations (ECLAMC) should help strengthen surveillance.

6. TAG recommends further research on testing algorisms and evaluation of alternative clinical specimens such as oral fluids and dried blood spots. Furthermore, indicators and strategies should be reviewed in the context of country experience with integrated surveillance. The impact of the rubella elimination initiative on strengthening health services, particularly services for women, should also be documented.

Laboratory

The PAHO Measles/Rubella Laboratory Network met to discuss a number of technical and logistical issues. Recommendations emerged relating to IgM kit selection, viral isolation and genotyping, preferred sample types, laboratory accreditation, classification of vaccine-related cases, treatment of false positives, treatment of suspected cases in pregnant women, and laboratory monitoring.

The final report and recommendations of the Measles/Rubella Laboratory Network are endorsed by the TAG (Annex 2).

Vaccination Strategies

1. TAG encourages the implementation of one-time mass vaccination campaigns in both men and women in all remaining endemic countries. The age group to be vaccinated, whether 15-29 years of age, 15-39 years of age, or else, should be determined based on the likely susceptibility of adults. This would depend on the year of introduction of the MMR vaccine in the national schedule, the extent of follow-up MR or MMR vaccination campaigns to maintain measles elimination, and the rubella epidemiology in the country. The TAG commends the countries that have successfully conducted adult mass vaccination campaigns.

   The countries that have conducted mass vaccination campaigns only in women will need to determine the extent of the virus transmission and susceptibility in men, and develop appropriate strategies to reduce the number of rubella-susceptible men.

2. Substantial evidence has accumulated from many studies, including recent studies in Brazil and Costa Rica, indicating that there is no identifiable link between vaccinating pregnant women and giving birth to a child with CRS. Therefore, there is no reason to modify the current approach of vaccinating all WCBA during campaigns. Brazil and Costa Rica should be congratulated on their studies and encouraged to submit their findings for publication.

Measles

In the 10 years since the goal of measles elimination was adopted, measles incidence has decreased by more than 99% in the Americas. Transmission of the D6 measles virus genotype—which began in 1995 and caused large outbreaks in Argentina, Bolivia, Brazil, the Dominican Republic, and Haiti—was interrupted in September 2001. The subsequent transmission of the D9 measles virus genotype in Venezuela was interrupted in November 2002, 14 months after it had started. The Venezuelan outbreak can be viewed as the last instance of widespread endemic transmission of the measles virus in the Americas.

In 2003 and 2004, approximately one hundred cases were reported each year in the Americas. Most of these cases were directly or indirectly linked to importations of the measles virus from other Regions of the world. One or more importations were also at the origin of the 108 measles cases that occurred in Mexico between April 2003 and April 2004; no new case has occurred thereafter. Measles virus of the same genotype (H1) was isolated in specimens of twelve patients who had fallen ill between May 2003 and March 2004. It cannot be determined whether the Mexican cases are part of a single transmission chain that continued for 13 months, or are the result of numerous, discrete importations. In 2003, the proportion of municipalities in Mexico with >90% coverage with measles-containing vaccine was 96%. The high coverage achieved in Mexico contributed to the containment of the outbreak.

As long as measles eradication is not pursued globally, imported or import-related measles cases will continue to occur in the Americas. However, the experience in several countries shows that, when high coverage with measles-containing vaccine exists, reliable detection and aggressive follow-up of suspect cases will limit the consequences of measles virus importations.

Besides its role in the early detection of suspected cases, surveillance can provide evidence of the absence of endemic measles virus transmission in the Americas. Consequently, national surveillance systems are the cornerstone of maintenance of interruption of measles transmission. Standardized surveillance indicators will allow a transparent and uniform evaluation of surveillance systems across the countries of the Region.

Two majors concerns:

1. Measles surveillance quality needs improvement

- The TAG recognizes that the achievements in measles elimination are in part a testimony to the quality of the surveillance systems implemented by countries of the Americas. However, surveillance can be improved.
- As of October 2004, none of the countries have met all six surveillance indicators. Seven countries met four or fewer indicators, and seven do not report/calculate indicators. However, the only indicator which has not been fulfilled consistently over

the last four years (i.e., regional average <80%) is timely submission of samples to the laboratory.
- An indicator describing measles/rubella surveillance sensitivity, such as AFP for poliomyelitis, has not yet been defined.

2. Forty-one percent of municipalities have <95% coverage of measles-containing vaccine

- In 2003, coverage of measles-containing vaccines was <80% in 20% of the municipalities in the Region and 80–94% in 21% of municipalities. Significant pockets of susceptible populations remain throughout the Region.
- As long as measles is still endemic in other Regions of the world, the Americas will need to sustain high coverage rates of measles-containing vaccine. Follow-up vaccination campaigns remain a required strategy to achieve that objective.
- The recent measles virus transmission in Mexico encourages all countries in the Region to improve immunization coverage and surveillance as the best protection against importations. The 20th Meeting of Health Ministers of Central America and the Dominican Republic (RESSCAD) decided in July 2004 to identify high-risk municipalities where intensive vaccination activities are to be conducted, to evaluate the necessity and feasibility of anticipating follow-up vaccination campaigns, and to enhance measles/rubella surveillance with inclusion of active case search.

Recommendations:

Recognizing that endemic measles virus transmission has likely been interrupted in the Americas, the TAG reaffirms the need for a continued commitment of health authorities and workers toward sustaining past achievements.

- To avoid outbreaks, coverage rates with measles-containing vaccine must be maintained at >95% in all municipalities. Improving coverage with the first dose may be accomplished through implementation of specific strategies in high-risk districts. High-quality nationwide follow-up campaigns should also be conducted every 3 to 4 years in order to maintain population immunity. Additionally, supplemental immunization activities should target low-coverage municipalities and under-served or hard-to-reach population groups.

- To harmonize practices among countries, the TAG endorses the definitions of elimination, re-establishment of endemic transmission and imported/import-related cases recommended by the Meeting of the Ad-hoc Panel of Experts in Rubella and Measles held in Washington, D.C. in March 2004, cited in the PAHO EPI Newsletter (EPI Newsletter: *Meeting of Ad-Hoc Panel of Experts in Rubella and Measles.* April 2004, Vol. XXVI (2), <http://www.paho.org/English/AD/FCH/IM/sne2602.pdf>). (Annex 1).

- To guarantee transparency and foster mutual trust, the TAG encourages countries to share with PAHO's Immunization Unit information on all aspects of their immunization programs. Such information includes, but is not limited to, case-based surveillance, laboratory data, and vaccine coverage data.

- Three surveillance indicators are particularly critical: proportion of suspected measles cases with an adequate investigation, proportion of suspected cases with an adequate blood sample, and proportion of transmission chains with representative samples for viral isolation.

- An indicator for rate of febrile eruptive illnesses investigated should be established, based on the experience in the countries.

- PAHO should review logistical and other issues which are barriers to submitting samples in a timely fashion.

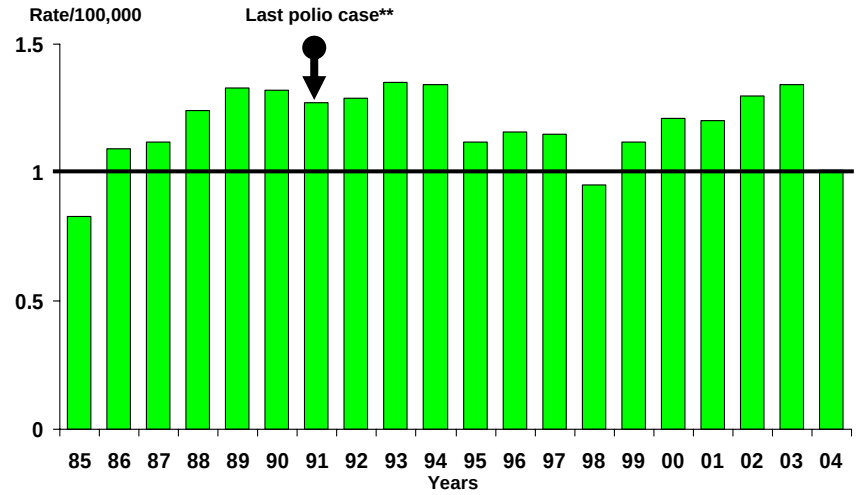
- The TAG recognizes the work of the Secretariat in updating the Measles Field Guide, as well as field guides for polio, rubella and other vaccine-preventable diseases, in 2004. The TAG encourages the use of these guides in training and updating the skills of health personnel.

- An ad-hoc group should be established to review past experience and to identify best practices in measles surveillance and vaccination.

Poliomyelitis

The eradication of polio from the Western Hemisphere was achieved in 1991 and the Region was certified as free of the circulation of the indigenous wild poliovirus in 1994. The countries of the Americas have taken steps aimed at achieving high polio vaccine coverage in every district, as well as promptly detecting the circulation of Sabin vaccine-derived viruses in the Region. The proportion of adequate specimens remains at approximately 80% and the rate of acute flaccid paralysis (AFP) continues to be above 1/100,000 children aged <15 years (Figures 3 and 4). However, the 2004 AFP rate for the Region has shown an alarming decrease compared to 2003.

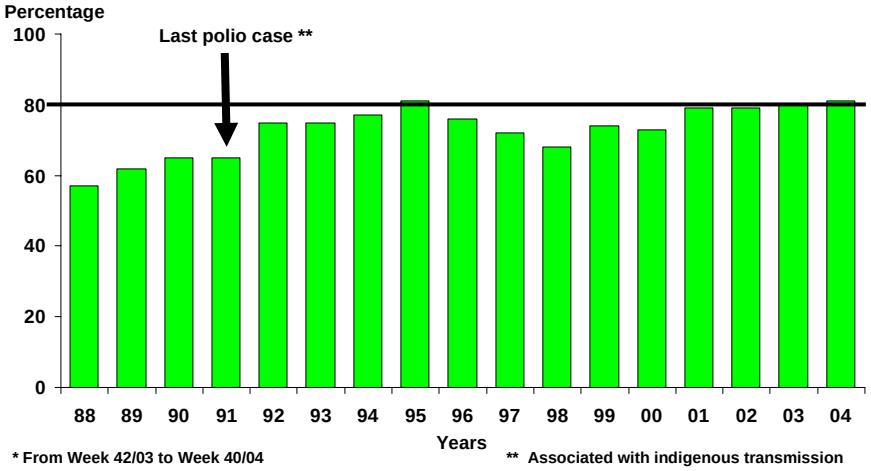
Figure 3. AFP rate per 100,000 children aged <15 years
Region of the Americas, 1995-2004*



* 2004: last 52 weeks (Week 39/03 to Week 37/04) ** Associated with indigenous transmission

Source: FCH-IM

Figure 4. Percentage of AFP cases with adequate stool specimens
Region of the Americas, 1988 – 2004*



* From Week 42/03 to Week 40/04 ** Associated with indigenous transmission

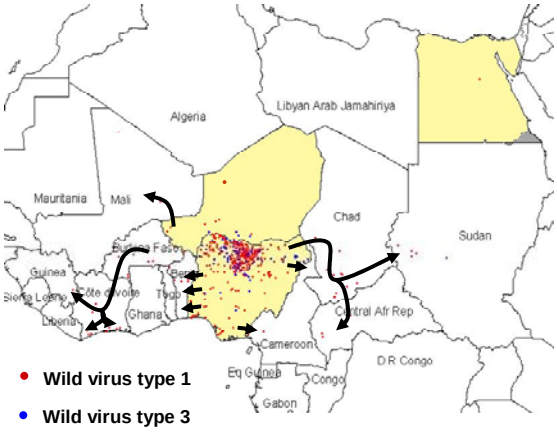
Source: FCH-IM

In 2003, a Sabin-derived poliovirus was isolated in an immunodeficient child in Peru. Intensive active case search and thorough review of district coverage were immediately conducted; no further AFP cases were identified and OPV coverage was found to be >95% in all surrounding areas. Follow-up stools for viral isolation were negative. The TAG commends the immediate response of the Peruvian Government and its expressed willingness to conduct a national mass campaign had the epidemiological circumstances proved necessary.

Several contributions of the Region of the Americas to the global polio eradication initiative should be commended, such as the IPV immunogenicity study conducted in Cuba, the study on immunization policy for the end-game, and the efforts to keep the Region free of poliomyelitis.

This past year, the global polio eradication initiative has made substantial progress. As of 1 September 2004, the intensified efforts in Asia and Egypt were progressing well. After a marked increase in campaign efforts, polio transmission in Afghanistan, India, Pakistan, and Egypt has been reduced. Just 61 cases have been reported since 1 January compared with 168 over the same period in 2003. In contrast, sub-Saharan Africa experienced epidemic polio; the number of cases in Nigeria and Niger soared to 495 (compared to 111 in 2003) and the virus spread to 12 previously polio-free countries (Figure 5).

Figure 5. Impact of OPV suspension, Nigeria
Poliovirus spread, 2004



Nigeria: 650 cases.

Polio re-established in 4 polio-free countries.

Kano, Nigeria restarted OPV use on 31 July.

The success of this intensified polio eradication effort in Asia and Africa now depends on (a) direct oversight by national authorities and participation by all political, traditional, religious and community leaders; (b) action by the international community to rapidly close the US$200 million funding gap for intensified eradication activities during 2004-2005; and (c) continued high-quality surveillance and routine immunization coverage in polio-free areas.

Recommendations:

- Countries of the Americas must maintain adequate AFP surveillance, sustain high OPV coverage in every municipality, strengthen the polio laboratory network, and comply with the Plan of Action for Laboratory Containment of Wild Poliovirus.

- The TAG reiterates previous recommendations and states that OPV must remain the vaccine of choice for the final phase of global polio eradication. OPV provides intestinal immunity, is substantially less expensive than IPV, is easy to administer, and protects contacts in the family and community, thereby conferring herd immunity.

- PAHO should not consider any change in current OPV policy of the Region until the world is certified polio-free.

- The Region should advance in the post-certification period in close accordance with the global policies stated by the Global Certification Commission on Polio Eradication.

- Ideally, all polio vaccination should be stopped globally after the world is certified polio-free. Based on an analysis of the risks and strategic options, in September 2003, a World Health Organization (WHO) Advisory Group recommended that plans be developed and steps be taken to prepare for the coordinated cessation of OPV use for routine immunization after the global interruption of wild poliovirus transmission. However, given that polio is still circulating in the world, the countries of Latin America and the Caribbean should continue to use OPV in their routine program to maximize population immunity until global polio eradication is achieved.

- An analysis of the vaccine-associated paralytic paralysis (VAPP) case incidence in the Region of the Americas should be presented at the next TAG meeting. That information should be used to better evaluate the risk that countries will face during the end game.

- PAHO should continue to more accurately define the cost-effectiveness of the post-certification vaccination options with concomitant analysis of opportunity costs.

- AFP cases need to be classified in a more timely fashion to reduce the unnecessary accumulation of pending cases being reported in the PAHO bulletin.

Laboratory

A PAHO Polio Laboratory Network meeting was held immediately prior to this year's TAG meeting. The objective was to evaluate the status of the network and to define actions to be taken in order to improve it. The TAG endorses the report of the Polio Laboratory Network Meeting (Annex 3).

- However, the TAG is especially concerned about the need to strengthen logistical and technical cooperation, and overall management of the PAHO laboratory network. It recommends that PAHO appoint a regional advisor to coordinate the polio laboratory network. This person would coordinate all technical and operational support pertaining to accreditation issues, logistics, and data management. The TAG also recognizes that IM will require two additional staff members to coordinate the other laboratory networks.

Neonatal Tetanus

The elimination of neonatal tetanus (NNT) as a public health problem has been achieved in the Americas. The incidence has dropped 95% from 1988 to 2003. Less than 0.07% of all districts still have an incidence rate above 1 case per 1,000 newborns. From 2001-2003, Haiti, with a population of only 8 million inhabitants, reported close to 50% of the total number of cases in the Region of the Americas. The annual number of cases for the Region was 1,470 in 1988; it fell to 157 in 2001, 122 in 2002, and 67 in 2003.

Implementation of the regional strategies, which first addressed high-risk districts and subsequently, other at-risk areas, has made it possible to focus the efforts of the health system to those groups and regions where the services have the greatest impact. The remaining cases are scattered throughout rural areas lacking adequate health facilities, and where extensive migration, lack of prenatal care, and poor sanitary conditions are prevalent.

The TAG reinforces its previous recommendations regarding NNT and considers that a single NNT case in the Americas should be considered a failure of the health services. All cases should be subject to thorough evaluation to determine how future cases can be prevented.

Haiti's national plan to eliminate maternal and neonatal tetanus aims to vaccinate 1.4 million WCBA in 59 high-risk districts (the country has 2.1 million WCBA and 133 districts). This initiative, a coordinated effort supported by the Interagency Coordinating Committee (ICC), started in 2003 with the vaccination of 50,000 WCBA. The efforts of Haiti should be fully supported by the international community.

Recommendations:

- Countries must maintain a >90% coverage of Td vaccine in WCBA in every district.
- An adequate surveillance system must be ensured to guarantee the accuracy of reported incidence of NNT.
- All NNT cases should be fully investigated. Information about the mother's age, immunization history, recent migration, missed opportunities to vaccinate and ethnic group should be used at the national and local level to identify remaining high-risk groups.
- The national plan to eliminate maternal and neonatal tetanus in Haiti must be implemented and deserves the full support of the international community. PAHO should continue to use every avenue available to assist Haiti in strengthening its health infrastructure.

Yellow Fever

During 2003-2004, countries with enzootic areas have made significant progress in preventing and controlling yellow fever in the Region. All enzootic countries have developed and are implementing national Plans of Action. However, some countries still require more political and financial support to accomplish their goals.

In 2003, 242 confirmed cases were reported to PAHO, with a case-fatality rate of 44%. The number of confirmed cases was three times higher than that reported in 2002. Over 80% of the cases were related to outbreaks in Brazil, Colombia, Venezuela, and Peru. Whereas the outbreaks in Colombia, Venezuela and Peru occurred in traditionally enzootic areas, the outbreak in Brazil was in an area that was not considered enzootic, and thus was not the object of vaccination activities. In 2004, yellow fever outbreaks have been reported in Bolivia, Colombia, and Peru; isolated cases have also been identified in Brazil and Venezuela.

Colombia and Venezuela implemented a contingency plan to respond to the outbreak that occurred during 2003-2004. Peru used the results of socio-anthropologic studies to focalize interventions in the traditionally enzootic parts of the country and expanded the target area to include zones that are the source of migration to enzootic areas.

The yellow fever vaccine is regarded as one of the safest vaccines. However, a few adverse events supposedly associated with the vaccine have been reported and are being investigated.

Recommendations:

- Countries with enzootic areas should view yellow fever as a public health priority, providing political, technical, and financial support for the implementation of national plans for yellow fever prevention and control.

- Epidemiological surveillance of yellow fever virus circulation should be strengthened both in enzootic and non-enzootic areas to allow rapid implementation of outbreak control measures when a human case or an epizootic is detected.

- To enhance the early detection of yellow fever virus circulation, the implementation of epizootic and febrile icteric syndrome surveillance in both enzootic and non-enzootic areas is advised.

- The yellow fever vaccination plan should target 100% of the population residing in enzootic areas and areas that are the source of migration into enzootic areas. Yellow fever coverage in these areas should be maintained at >95% among children aged 1 year, as should measles coverage.

- The maintenance of low infestation rates of *Aedes aegypti* is important, not only to prevent the reurbanization of yellow fever, but also to avoid extensive outbreaks caused by the dengue virus.

- An adequate yellow fever vaccine stock should be maintained both for the regular program and campaigns, with reserves for control of possible outbreaks.

- Epidemiological monitoring of adverse events attributable to the yellow fever vaccine should be strengthened.

National EPI Evaluations

Evaluations of national Expanded Programs on Immunization (EPI) have been promoted by PAHO since the 1980s. They have been implemented on a more frequent basis since 1996. These evaluations, conducted by a team composed of national authorities and international partners, allow the identification of strengths and weaknesses in every component of the national EPI. Specific recommendations for program improvement are the outcome of these evaluations.

The national EPI evaluations have proved to be a useful tool to guide EPI planning and to define specific actions. They also boost the political prominence of the EPI at the national level. As seen in Bolivia, repeated evaluations allow monitoring of EPI progress over time.

The following table presents the principal strengths and weaknesses of select national EPIs in 2002-2004:

Country	Main Strengths	Main Weaknesses
Antigua and Barbuda	• Good community participation • Vaccination registries	• Financial problems to sustaining EPI • VPD Surveillance system needs to be strengthened
Belize	• Overall organization, coordination and programming	• Training and supervision • Surveillance of non-measles/rubella VPDs
Bolivia	• Efforts to improve the EPI at all levels • Operational research and laboratory	• Insufficient resources for planned programs • Weak and incomplete notification of VPDs
Dominica	• The program is well planned and executed	• VPD surveillance system needs to be strengthened
Jamaica	• Vaccination registry, coordination with schools and activities to reach defaulters	• Barriers limiting access to vaccines • Staff shortages and local coordination/organization issues
Nicaragua	• Successful National Health Weeks • Efficient local level activities	• Data quality and information not always used for action • Some injection safety issues

<u>Recommendations</u>:

- PAHO should continue to conduct national EPI evaluations in the Region and promote the use of the results as a tool to elaborate annual EPI Plans of Action, as well as to strengthen strategic alliances. Also, repeated national EPI evaluations should be used as an instrument to evaluate progress over time.

- The TAG recommends refining the performance criteria for political commitment in view of regional progress. Political commitment cannot be assessed solely by the presence of a vaccine law and/or national budget line item for vaccines in the country. Staffing levels and the amount of resources assigned to logistical support should also be considered.

Vaccination Safety

As the incidence of vaccine-preventable diseases is reduced, thanks to effective vaccination programs, adverse events supposedly attributable to vaccination or immunization (ESAVI) will become more prominent. In 2003, immunization safety training workshops were held in Peru, Ecuador, and the English-speaking Caribbean. Participants from 21 countries attended, including 183 professionals from the areas of immunization, epidemiology, and communications, as well as representatives from the national regulatory authorities. More than 900 professionals participated in replications of those workshops at the country level, which lead to the formation of national teams to investigate adverse events. The teams have improved the quality and speed of investigations, and have also improved management of ESAVI from a clinical, laboratory, epidemiological, and communications standpoint.

Results of Survey Pertaining to Use of Vaccination Safety Devices

A survey was conducted in 2003, in which EPI managers responded to a standardized questionnaire on vaccination safety in their respective countries. Venezuela, Uruguay, Paraguay, Honduras, Guatemala, El Salvador, Colombia, Bolivia, and Peru participated.

Vaccination Safety Components Used in National EPI	% Respondents Using the Components
Auto-disable (AD) Syringes	30%
Disposable Syringes	100%
Safety Boxes	30%
Disposable Plastic Receptacles	40%
Both Forms (safety box & disposable plastic receptacle)	30%
No Recapping of Needle Syringes	75%
Open Vial Policy Recommended by PAHO/WHO	100%
ESAVI Monitoring Systems	70%

Progress is clearly being made, but much remains to be done to improve immunization safety.

Recommendations:

- In order to measure progress in the implementation of the monitoring system for vaccination safety in the countries, the following indicators have been proposed: percentage of serious adverse events investigated within 24 hours and the rate of

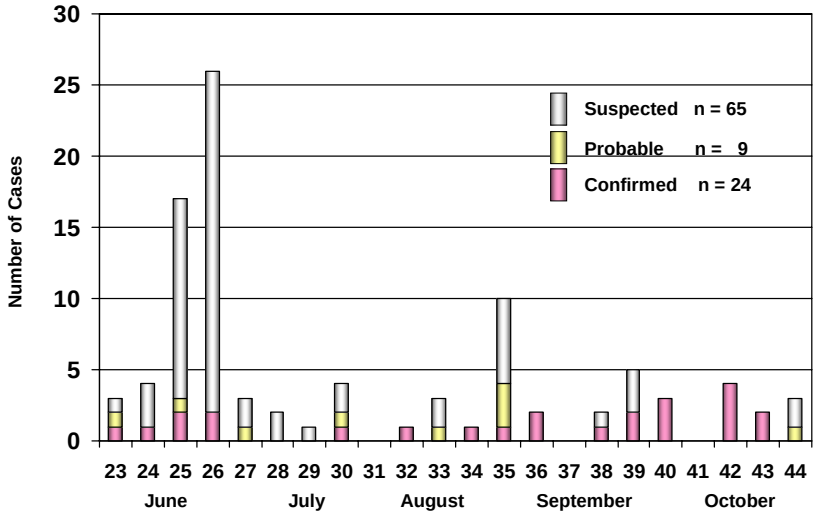
adverse events classified as program errors. At the next TAG meeting, country experiences in using theses indicators should be presented and evaluated.

- Environmental regulations should be developed and enforced, as they are crucial to promoting appropriate disposal of needles and syringes.

Diphtheria

Sporadic cases of diphtheria occur in Haiti almost every year. Six cases were reported in 2002, two in 2003. In June 2004, a large cluster of cases was reported in the area surrounding Fond des Blancs, a market town in a mountainous rural area in the southwestern part of the country. This cluster included 56 cases seen at a local hospital, with onset dates in June or July. Anecdotal reports of numerous other cases—including some deaths—in these communities were also received. In addition, isolated cases were reported in other parts of the country. An investigation was conducted to confirm and characterize the reported diphtheria outbreak (figure 6). Between June and October 2004, 98 suspected cases of diphtheria were reported. Of those, 24 were confirmed; mortality rate was 46%. Nine of the reported cases were classified as probable and the remaining 65 as suspected.

Figure 6. Diphtheria Epidemiological Curve, Haiti, June – October, 2004



Data up to 3 November 2004

Source: Ministry of Health, Haiti

The diphtheria outbreak in Haiti highlighted the need to strengthen the routine immunization program, which in 2003 achieved only 48% DPT3 coverage in children aged <1 year.

<u>Recommendation</u>:

- Occurrence of endemic diphtheria is evidence of low vaccination coverage. Experience from the outbreak in the former Soviet Union indicates that mass vaccination campaigns directed at susceptible age cohorts are effective in stopping diphtheria. Therefore, countries with diphtheria are encouraged to take an aggressive approach to improving coverage with DTP vaccine through a combined approach of mass vaccination efforts and strengthening of routine services.

Pertussis

Pertussis is a highly transmissible bacteria (up to 90% in susceptible individuals) that affects all age groups. As such, areas of high population concentration and migration, such as the U.S.-Mexico border, are at particular risk. In 2003, a border outbreak began, resulting in 29 confirmed pertussis cases over four months. The first case—a six-week old female infant from Alpine, Texas—was reported by an intensive care hospital unit in Lubbock, Texas on 23 September 2003. A case investigation was initiated the same day and, during the next four months, 197 contacts received prophylaxis. Three infants, all under six weeks old, died of pertussis infection during the outbreak.

Analysis of the data collected during the investigation suggests that several factors contributed to the outbreak. A large number of susceptibles due to low vaccination coverage was one of the primary causes; other factors included sub-optimal vaccine efficacy, persistent adult carriers with minimal symptoms, and poor coordination of cross-border case management.

Recommendations:

- To prevent pertussis outbreaks, high vaccination coverage must be achieved and maintained at the district level. Countries are encouraged to strengthen surveillance and laboratory capacity to confirm diagnosis through culture of *B. pertussis*, thereby contributing to stronger surveillance.

- PAHO should encourage the use of World Health Organization (WHO) standardized case definitions and surveillance and laboratory guidelines.

BCG Vaccination

The World Health Organization (WHO) estimates that in 2000 there were 1.8 million deaths due to tuberculosis and 8.3 million new cases. Control of tuberculosis includes the use of BCG vaccine, as well as identifying and treating tuberculosis cases. BCG vaccination does not prevent initial infection but exerts a protective effect against disseminated, or miliary, tuberculosis, and tuberculous meningitis. WHO, PAHO, and the International Union Against Tuberculosis and Lung Disease (UNION) recommend that a single dose of BCG be given at birth, or as early as possible in the first year of life. Most children who develop the severe tuberculosis that EPIs hope to prevent with BCG vaccination become infected in the first years of life. Available data indicate that BCG given as a first dose after the first year of life may be less effective than a BCG first dose given sooner after birth.

Since 1995, revaccination has not been recommended based on the lack of definitive evidence that repeated BCG vaccination confers additional protection against tuberculosis, although it may be protective against leprosy. Revaccination schemes often target children aged 5 to 15 years, an age group with low rates of infection and low rates of severe disease. Thus protection conferred by BCG vaccination in this age group is variable at best.

Recommendations:

- Countries should vaccinate with BCG at birth since it increases protection against severe disease in the first year of life.

- Primary vaccination with BCG after the first year of life is not recommended as the protection afforded is less than when given at birth.

- Those children with a documented dose of BCG who do not develop a scar do not need to be revaccinated.

- The TAG supports the WHO and UNION recommendation not to revaccinate or administer booster doses.

Vaccination Week in the Americas (VWA)

Vaccination Week in the Americas (VWA) began as a proposal by the Ministers of Health of the Andean Region, in response to a measles outbreak that occurred in Venezuela and Colombia in 2002. This annual event was endorsed by PAHO's 44th Directing Council in 2003 through Resolution CD44.R1. The underlying principles of the VWA are equity, access, and pan-Americanism. Vaccination activities target indigenous populations and ethnic minorities, municipalities with low coverage, and areas that are remote, around borders, or on the urban fringe.

In 2003, 19 countries of South America, Central America, and the Caribbean participated in the first VWA. These countries vaccinated 13,583,888 children aged <5 years and approximately 2,700,000 WCBA. By 2004, this event grew to include 35 countries and seven territories in the Americas. Forty-three million people were vaccinated, including 15 million children aged <5 years, 9 million adults aged <60 years, 13 million adults aged ≥60 years, 3 million WCBA, and 2 million individuals from other risk groups. Of the 15 million children aged <5 years who received the DPT vaccine, approximately 23% had not previously received any vaccine dose.

An essential element of the VWA has been the formation of strategic partnerships and the strengthening of interagency cooperation at both the regional and international levels. PAHO, the Centers for Disease Control and Prevention (CDC), the United Nations Children's Fund (UNICEF), and many other organizations combined technical and financial efforts to support activities in the countries. The VWA coincided with the National Child Vaccination Week of the CDC, enabling PAHO and the CDC to combine their slogans to promote their efforts more widely throughout the Americas. The themes "Vaccination: An Act of Love" and "Love them; protect them; vaccinate them" were used together in much of the published literature.

There was excellent trans-border coordination, resulting in more than 22 bi-national launches together with a regional launch along the border between Haiti and the Dominican Republic. Five presidents, several first ladies and Ministers of Health, and many community leaders participated in the launching of the VWA and other activities.

An evaluation of the impact of the VWA was conducted in Paraguay and Nicaragua. The results showed an increase in vaccination coverage in under-served areas, as well as detecting important factors that will improve the performance and quality of the immunization programs.

The VWA is an opportunity to strengthen interagency and intersectoral cooperation, non-governmental organization involvement, and participation from the private sector. It also contributes to strengthening border activities among countries.

Recommendations:

- Guarantee the sustainability of VWA by including it within the national EPI Plans of Action and using it to support rubella/CRS elimination in the Region.

- Maintain the VWA as a strategy to strengthen immunization programs throughout the Region, increase visibility, and encourage advocacy in the political agenda.

- Target interventions in population groups traditionally under-served.

- Through operational evaluations, document the reduction in vaccination inequities by determining VWA contributions reaching zero-dose children.

Influenza

Influenza is a viral disease that affects millions of people and kills approximately one million people worldwide every year. The age groups most affected are children aged <2 years and adults aged >60 years. Many of these cases and deaths can be averted through the use of safe and effective vaccines.

The Region has experienced success with regard to routine vaccine use in older adults, chronically ill or immunodeficient individuals, health professionals, pregnant women, and, more recently, children aged ≤23 months. Studies on disease burden, cost-effectiveness, and vaccine impact are being conducted to assist decision-makers on the introduction of new vaccines and maintenance of routine immunization at the national level.

Recommendations:

- Countries should establish and strengthen epidemiological surveillance of influenza and other acute respiratory infections to determine the characteristics of virus circulation in the countries. This recommendation is particularly important in tropical areas where more information is needed to understand the pattern of viral circulation. Gathered information will guide adequate vaccine formulation appropriate timing for vaccine administration; it will also allow countries to better measure the impact of the intervention.

- PAHO recommends that older adults, chronically ill individuals, immunodeficient populations, health professionals, pregnant women, and children aged 6-23 months be vaccinated; priority should be given to people aged ≥60 years.

- Countries should conduct studies that document the disease burden and economic impact of annual influenza epidemics. It is anticipated that results will support influenza immunization policies within the context of other national health priorities.

- All the countries of the Region should develop plans, in accordance with WHO guidelines, to respond to an influenza pandemic. The recent epizootic in Asia, with the occurrence of human cases of avian flu, characterized by high case-fatality rate, demonstrated the need for countries to be prepared for a possible pandemic.

- To help countries deal with the challenges related to influenza vaccine, PAHO should convene a group to consider issues of vaccine development, production, and procurement, and to make recommendations.

Haemophilus influenzae type b (Hib)

Considerable progress has been made with the introduction of the vaccine against *Haemophilus influenzae* type b (Hib) in the Region. More than 95% of the countries have included the vaccine in routine immunization programs, obtaining high levels of vaccination coverage and a significant reduction in the incidence of the disease.

The availability and use of vaccines that combine Hib with DTP simplifies the administration of antigens against the principal childhood diseases, decreasing the risk of adverse events (such as needle stick injury), lost opportunities for vaccination, and required number of visits.

Recommendations:

- Countries that are not yet using the Hib vaccine should make every effort to introduce it into their routine immunization programs.

- Countries that are already using the Hib vaccine should monitor and report vaccination coverage and Hib cases in order to evaluate the impact of the intervention.

- The TAG recommends establishing sustainable financial mechanisms to maintain vaccination against Hib. Purchasing this vaccine in combination with DTP or DTP/HepB through the PAHO Revolving Fund can result in significant cost-savings and thus improving sustainability.

New and Under-utilized Vaccines

Vaccine development is progressing rapidly. Several new vaccines are available for use in the prevention of infectious diseases that are considered serious public health problems in the Region of the Americas.

When the introduction of new vaccines is considered, the following issues should be addressed: disease burden, risk groups, studies of cost-effectiveness, vaccine availability, possible adverse events attributable to the new vaccine, the vaccine's impact on national budget and cold chain, effects on the vaccination schedule, adequacy of surveillance, political commitment, and financial sustainability. These are fundamental considerations for all countries that are considering the introduction of new vaccines.

Recommendations:

- All countries of the Region should continue to develop disease surveillance systems. The captured information will help estimate disease burden and provide mechanisms for public health interventions. The TAG identifies as a priority surveillance for influenza, pneumococcal disease, meningococcal meningitis, rotavirus infection, hepatitis A infection, and varicella-zoster infection.

- All national EPIs should establish scientific advisory committees to assess risks and benefits and prioritize issues related to vaccine introduction.

- National committees on immunization practices (NCIP) should participate fully in this assessment process. Special attention should be given to financial sustainability when new vaccine introduction is being considered.

- Once a new vaccine is introduced, TAG emphasizes the commitment to maintain a permanent vaccine supply and surveillance activities to monitor the impact of the intervention.

New and Under-utilized Vaccines (Rotavirus)

Rotavirus (RV) is one of the most common causes of severe diarrhea worldwide and accounts for >600,000 estimated deaths per year (approximately 5% of all deaths among children aged <5 years). Of those, 82% occur in developing countries.

In the Region of the Americas, RV diarrhea constitutes an important public health problem in a majority of the countries, causing >15,000 deaths and 75,000 hospitalizations per year.

Two vaccines are about to enter the market. One vaccine is derived from a single strain of human rotavirus of serotype G1, one of the most common strains in circulation. The virus has been attenuated by repeated cell culture passages. Preliminary results from studies have indicated that the vaccine is safe and has an efficacy >84% against severe rotavirus disease. The second vaccine is a reassorted bovine-human strain that includes the main neutralization antigens from the five major rotavirus serotypes in circulation (G1-G4 and P1). Preliminary data indicate that this vaccine will also be safe and effective in preventing severe rotavirus diarrhea.

Although the prospects of rotavirus vaccine introduction are encouraging, a vaccine would only solve the problem partially. Primary health care interventions that address less severe RV diarrhea and diarrhea from other causes will remain important.

At the 6th International Rotavirus Symposium in Mexico in July 2004, representatives of Ministries of Health called upon PAHO and the PAHO Revolving Fund to facilitate the introduction of vaccines against rotavirus, at prices accessible to all countries of the Region and as soon as a vaccine becomes available.

Recommendations:

- PAHO should support the rotavirus accelerated studies and epidemiological surveillance that have been initiated in some countries of the Region. Those countries that have not begun studies should do so as soon as possible, following the WHO generic protocol for rotavirus surveillance.

- Methodology for economic studies such as cost-benefit and cost-effectiveness should be standardized to facilitate comparison between countries.

- A surveillance database should be created to enable comparison of results from different studies in the Region. The database would be similar to those that exist for polio, measles and rubella. Identification of the most frequent rotavirus genotypes and serotypes circulating in the Region will help to better define the most appropriate vaccine.

- PAHO should convene a meeting of Ministers of Health and Ministers of Finance of 10-12 countries in the 1st half of 2005 to discuss the economics of RV vaccine introduction.

- Final results on vaccine safety need to be thoroughly evaluated.

New and Under-utilized Vaccines (Pneumococcus)

Many world leaders do not recognize that pneumonia is the leading cause of death in children, higher than HIV, TB or malaria. Globally, pneumococcal disease is estimated to cause 1.6 million deaths, 800,000 of which occur in children.

The rates of invasive disease are highest in children aged <2 years, but disease continues to occur in other age groups and particularly among the elderly. In industrialized countries, the disease has the highest mortality rate among the elderly.

During the Regional Workshop on Epidemiological Surveillance of Pneumococcus in the Region of the Americas, held in Mexico City, Mexico on 2 November 2004, the current status of pneumococcus surveillance in the Region was reviewed.

Pneumococcal research in the Americas dates back to the 1993 establishment of the Sistema Regional de Vacunas (SIREVA) project for surveillance of pneumococcal disease. The objective of the SIREVA network was to conduct pneumococcus surveillance and to determine serotype prevalence and antimicrobial resistance patterns of pneumococcus. Subsequently, SIREVA was incorporated into the PAHO Special Program for Vaccines and Immunization (later transformed into the PAHO Division of Vaccines and Immunization), which expanded the activities of the network to other agents, such as *Haemophilus influenzae* type b (Hib) and meningococcus. In 2000, surveillance activities were further enhanced by adding surveillance for radiological pneumonia.

Based on data collected in six countries, no significant serotype changes occurred from 1993-1999 to 2000-2003. In all, over 4,000 isolates were studied in each period. Serotype 14 was the leading serotype isolated in most countries. Based on local serotype data, the 7-valent vaccine would cover 65% of serotypes, 9-valent would cover 77% and 11-valent would cover 83%. Surveillance of sensitivity to antibiotics showed that penicillin resistance increased from 14.7% in 1993 to 30.6% in 1999. By 2000-2003, resistance had gone up to 39.8%.

The impact of the conjugated heptavalent vaccine in children aged <1 year was evaluated in the municipality of Almoloya, State of Hidalgo, Mexico. Vaccine was administered according to the following recommendations: 3 doses plus a booster dose for children aged 2-6 months and 2 doses plus a booster dose for children aged 7-11 months. A follow-up of 185 children showed that 32% were carriers of *Sp. pneumoniae*. Six of the seven vaccine serotypes were isolated (4, 6B, 14, 18C, 19F, and 23F). Results demonstrated a decrease in the serotypes with high resistance to penicillin, as well as a decreasing trend in mortality due to pneumonia and acute respiratory infection.

Population-based studies using health facilities with well-defined catchment populations are valuable in determining the incidence of pneumonia. A combined approach of using clinical criteria and radiological image facilitates the diagnosis of

probable bacterial pneumonias. Nevertheless, only three studies in Brazil, Uruguay and Argentina - all supported by PAHO and PATH - have been completed.

Recommendations:

The following recommendations, which particularly relate to surveillance, are made for countries considering the introduction of pneumococcal vaccine. PAHO will need additional financial support if it is to successfully coordinate them.

- Strengthen the overall laboratory capacity to maintain the high level of performance acheived thus far by the surveillance network.

- Strengthen the clinical and epidemiological components of surveillance.

- According to capacities, undertake one or more of the following at key surveillance centers:
  - Economic studies;
  - Surveillance of pneumococcal disease in adults; and
  - Strengthening of population-based component.

- Support PAHO's role in the regional coordination for oversight of the surveillance network, including country meetings, mobilization of pediatric societies, and supervisory site visits.

New and Under-utilized Vaccines (HPV)

Carcinoma of the uterine cervix remains a significant cause of morbidity and mortality among women in the Region of the Americas. Although a human papillomavirus (HPV) vaccine for the prevention of cervical cancer is not yet available, PAHO must encourage member countries to discuss advancement made in this area. At the appropriate time, countries should start rational planning for vaccine introduction, focusing on surveillance and disease burden.

ANNEXES

ANNEX 1

EPI Newsletter

Expanded Program on Immunization in the Americas

Volume XXVI, Number 2 **IMMUNIZE AND PROTECT YOUR CHILDREN** April 2004

Meeting of Ad-Hoc Panel of Experts on Rubella and Measles

Some members of the Expert Panel (from left to right): Dr. Carlos Castillo-Solórzano, Dr. Peter Strebel, Dr. Louis Cooper, Dr. Stanley Plotkin, Dr. Michael Katz, Dr. Alan Hinman, and Dr. Jon Andrus. Washington, D.C., 3-4 March 2004.

During its September 2003 session, PAHO's 44th Directing Council endorsed the goal of rubella and congenital rubella syndrome (CRS) elimination by 2010 and urged countries to draft national plans of action within one year. It also requested the Director of the Organization to elaborate a regional plan of action and mobilize resources in support of the rubella and CRS elimination goal.

These recommendations were based on rapid reduction in diseases burden from the implementation of an accelerated rubella control strategy; the extensive experience gained by the Region in vaccinating large and heterogeneous population groups; the cost-benefit data from the English-speaking Caribbean; the availability of a safe, affordable, and efficacious vaccine; and the existing political commitment of Member countries.

Within this context, PAHO's Immunization Unit (IM) held a Meeting of an Ad-Hoc Panel of Experts on Rubella and Measles in Washington, D.C., from 3-4 March 2004. The goals of the meeting were to review the current strategies for rubella and CRS elimination, review current PAHO measles surveillance indicators and definitions for measles elimination, and make suggestions for revisions where needed.

The meeting brought together experts and health officials from Brazil, Canada, Chile, Honduras, Mexico, the United Kingdom, and the United States. PAHO IM staff and consultants, as well as staff from WHO, also attended. The experts reaffirmed that the strategies to eliminate rubella and CRS being advocated by PAHO are correct. These include routine high-level coverage of children; mass vaccination campaigns of adults to reduce the pool of susceptibles; inclusion of rubella vaccine in "follow-up" measles campaigns; and high-quality surveillance of rubella and CRS.

A table on the following two pages lists several of the issues addressed by the experts.

→ What definition of rubella elimination should be used in the Americas?	• Elimination of rubella and CRS in the Americas is the interruption of endemic rubella virus transmission in all countries. There are no indigenously acquired cases of CRS. • Re-establishment of endemic transmission is a situation in which a chain of transmission continues uninterrupted for a period ≥12 months. • Other definitions and classifications should be comparable to those established for measles.
→ Is there any reason to modify the current approach to vaccination of women of childbearing age?	• Experience in mass vaccination of millions of women of childbearing age has allowed follow-up of several thousand women who were vaccinated without being aware of pregnancy. Follow-up of their pregnancies has yielded very reassuring results. Although ~3.6% of infants born to susceptible women vaccinated in early pregnancy were IgM positive, **NONE** had anomalies compatible with congenital rubella syndrome. Virus isolation studies are continuing. • Other countries undertaking mass vaccination of adult women should conduct similar studies.
→ What are the potential benefits of the rubella initiative on strengthening the health system?	• Helps strengthen surveillance and services to newborns (e.g., hearing screening, birth defects surveillance). • May potentially improve services and follow-up to children with birth defects such as impaired hearing and learning disabilities. • Provides contact between official health services and adults, particularly adult males, who often are not in contact with these services. • Increases awareness of health issues for women. • Offers an opportunity to link child health and child education services. • Strengthens infrastructure and quality of services. • Creates cost savings for the health system. • Helps establish structure/mechanism for introducing future vaccines for use in adults (e.g., HIV, human papillomavirus).
→ Given the program will be moving to integrated measles/rubella surveillance, do the current case definitions need to be modified? If so, to what?	• Full integration of measles and rubella surveillance requires definition of a suspected measles/rubella case. Since younger health care workers are not familiar with measles, the following is proposed for a case definition: *a fever and rash illness or when a health care worker suspects measles or rubella infection.* • All notified suspected cases should be reported to the EPI notification system as well as to standard disease surveillance systems.
→ What criteria/indicators should be used/ established to document the adequacy of integrated surveillance?	• For purposes of discussion, integration is defined as not having totally separate reporting / surveillance systems for measles and rubella. Except for outbreak settings, all specimens will be tested for both measles and rubella. • Indicators should be developed for adequacy of combined / integrated measles / rubella surveillance. Many of the existing measles indicators can be used as is; some may require modification. • An important indicator of sensitivity of surveillance is the reported rate of suspected cases. It would be useful to have a minimum indicator of sensitivity comparable to the AFP rate used in polio. Participants asked that national experiences be reviewed so that proposals for a baseline rate could be discussed at the November 2004 Technical Advisory Group on Vaccine-preventable Diseases (TAG) meeting (i.e. 1-5/100,000 is being used in Mexico and the United Kingdom). The age group to which the baseline rate would be applied also needs to be established. • An indicator of specificity of surveillance relates to the results of lab testing.
→ Are the case definitions for surveillance of CRS useful?	• Case definitions for surveillance of CRS are very useful. It must be remembered that there is a difference between surveillance and diagnosis. A sensitive definition for reporting suspected CRS to trigger investigation is important in the context of elimination. The present definition appears adequate for surveillance: *a health care worker at any level of the health care system should suspect CRS in an infant when (1) One or more of the following birth outcomes are detected: congenital cataracts, hepatosplenomegaly, patent ductus arteriosus, purpura, or hearing impairment and (2) An infant's mother was known to have had laboratory confirmed rubella infection during pregnancy **AND** after a thorough physical examination, for any reason, there is clinical suspicion of CRS in the infant.* For diagnosis, a more specific definition might be appropriate. Laboratory confirmation remains the gold standard. • For purposes of monitoring trends, CRS surveillance should be strengthened throughout the Americas through collaboration with the regional Perinatal Information System from CLAP (Latin American Center for Perinatology and Human Development) and the ECLAMC (Latin American Collaborative Study of Congenital Malformations).
→ What should be the guidelines for CRS case investigation and follow-up?	• The present system of sentinel CRS surveillance is appropriate for countries in early stages of elimination activities. As the program matures, surveillance should probably extend to secondary hospitals as well as tertiary centers. In the end stages, attempts should be made to identify/investigate every case.

2

→ Are there additional tests or collection methodologies that should be incorporated into the laboratory network system? → For elimination purposes, when should a second specimen to measure IgM be collected? Are there any special groups in which test samples should routinely be repeated? → What is the appropriate use of IgM and avidity tests in pregnancy?	• Serum IgM testing within 5 days of rash onset may be negative in persons who are infected with rubella. For surveillance purposes of identifying chains of transmission, this is adequate in the earlier stages of elimination activities but will not be as elimination is approached. • In later stages, it may be necessary to take a second specimen if the initial IgM test (taken within 5 days of rash onset) is negative. This will allow testing of paired sera for both IgM and IgG. • Assessing suspected rubella in pregnant women will require taking a second specimen if the initial IgM taken within five days of rash onset is negative. This will allow testing of paired sera for both IgM and IgG. • Avidity testing can be a useful adjunct to IgM testing in assessing how recently infection occurred. However, it may not be helpful in re-infection, which may result in an IgM response. • In some areas of some countries, pregnant women are routinely tested for both IgG and IgM antibodies. Unless there is a suspicion of recent exposure to rubella, IgM testing should not be done because of the low, but real, possibility of false positivity or true detection of persistently positive IgM circulating antibodies. • Studies to assess the utility of other approaches to diagnosis, including RT-PCR (reverse transcriptase-polymerase chain reaction) testing of oral fluids or other pharyngeal samples, should be pursued actively by PAHO. At the same time, the practical issues involved in widely disseminating PCR testing need to be addressed.
→ What should be the guidelines for obtaining specimens for rubella virus culture?	• In countries where the incidence of rubella is still high, specimens should be obtained from a range of settings sufficient to establish the distribution of circulating strains of rubella virus. • In every country, one or more persons should be identified with the responsibility to assure collection of specimens for rubella virus isolation. This could well be the person responsible for measles virus isolation. • As elimination is approached, efforts should be made to isolate rubella virus from all sporadic cases and from every chain of transmission, both for diagnostic purposes and to characterize the origin of the virus. • Isolates obtained from these efforts should be characterized to enable appropriate use of molecular epidemiology. • Development of, for example, oral fluid (or other pharyngeal sample) RT-PCR technology could obviate the need for virus isolation for purposes of diagnosis.
→ What are the most appropriate definitions of measles elimination and re-establishment of endemic/indigenous measles transmission for use in PAHO?	• Measles elimination in the Americas is the interruption of endemic measles virus transmission in all countries. • Re-establishment of endemic transmission is a situation in which a chain of transmission continues uninterrupted for a period $\geq$ 12 months. • Imported cases are cases exposed outside the Western hemisphere during the 7-21 days prior to rash onset as supported by epidemiological and/or virologic evidence. • Measles import-related cases are locally-acquired infections occurring as part of a chain of transmission originated by an imported case as supported by epidemiologic and/or virologic evidence. • Measles cases with unknown source of infection are cases where source has not been identified after a thorough investigation.
→ Are the surveillance indicators proposed by PAHO appropriate?	• An indicator for rate of rash illness investigated should be established, based on the experience in the countries. • Current indicators appear useful.
→ What surveillance criteria in PAHO should be used to assess interruption of indigenous transmission (post-eradication)?	• A range of indicators will be needed, including level of population immunity, adequacy of surveillance and investigation, laboratory capacity and performance.
→ What criteria in PAHO should be used to certify measles elimination?	• In addition to criteria relating to duration of interruption of transmission and other factors mentioned above, operational criteria relating to program performance will be needed (e.g., review of clinic registries).
→ What should be the priority research issues for rubella and measles elimination?	• Impact of rubella program on routine immunization services and on strengthening health services. • Epidemiologic/economic implications of immunizing adult males in rubella programs. • Document the health/economic burden of rubella and CRS in the Americas and the costs and benefits of rubella elimination. • Document the impact of rubella and rubella elimination on sectors other than health – e.g., education. Evaluate tests (e.g., RT-PCR, avidity testing), alternative clinical specimens (e.g., oral fluid, dried blood spots), and testing algorithms in PAHO countries. • Review country experience with surveillance indicators/strategies. • Evaluate different approaches to CRS surveillance. • Evaluate the hemispheric Vaccination Week. • Review surveillance of events supposedly attributable to vaccines and immunization (ESAVI) and injection safety practices in PAHO.

3

ANNEX 2

MEETING OF THE MEASLES/RUBELLA LABORATORY NETWORK
2 November 2004, Mexico City

The PAHO Measles/Rubella Laboratory Network met for a one-day meeting on 2 November 2004 to discuss several technical and logistical issues. The considerations and recommendations from this meeting are as follows:

1. Test characteristics (i.e.,sensitivity and specificity), cost, practical aspects of performing the test, and epidemiology of other febrile rash illnesses are all important for evaluating and selecting appropriate rubella IgM kits.

2. For rubella IgM testing, kits A and B have an overall specificity equivalent to kits C, D, and E, but the former two kits had a higher proportion of false positive results with dengue positive sera. This should be taken into account when selecting kits to use in countries with known dengue circulation. It is therefore recommended that the Laboratory Network currently use either the C or D kit.

3. Rubella and measles molecular epidemiological data are useful for tracking transmission pathways, investigating suspected vaccine-related cases, documenting elimination of endemic strains, and supporting hypothesis of case importation from other Regions.

   For rubella, viral isolation and genotyping is currently important to establish the genotypes endemic in the Region. For measles, genotyping is currently important for documentation of importations, and differentiation of wild-type and vaccine viruses.

   A training course for rubella viral isolation/detection should be held in 2005.

4. Nasopharyngeal samples or throat swab are the preferred sample for viral isolation/detection for both measles and rubella viruses; urine samples are an acceptable alternative. Collection of both samples increases the likelihood of viral isolation/detection. Specimens for viral isolation/detection should always be collected on first contact with a patient.

   A virus genotype should be determined for all chains of transmission. In larger chains of transmission, such as in outbreaks, this will require collecting representative specimens for viral isolation.

CRS patients can excrete rubella virus for up to one year after birth (isolation rate 62% at 1-4 months of age, 11% at 8-12 months of age). Every CRS case should have rubella virus isolation/detection attempted.

5. The consensus was that accreditation and implementation of laboratory quality systems is very important for quality surveillance. Through regional coordination, PAHO should make a timeline for the accreditation process.

   A specific concern was the financial implication for countries to ship samples for confirmatory testing to the reference laboratories.

   A process for implementing simple accreditation criteria is needed. To begin, PAHO should adapt the WHO accreditation checklist. The adapted checklist can then be used as a starting point for accreditation.

   The group recommends having a workshop on "Management of Quality Laboratory Practices" in 2005.

6. In addition to laboratory results, criteria to classify a case as vaccine-related should include epidemiological information, time between vaccination and illness onset, and time between illness onset and sample collection. Thorough review of published literature and country experience is recommended to establish the specific timeframe in which effects are to be expected after vaccination. The end product of this work should be a regional guideline which harmonizes the various approaches currently followed by the countries in the Region.

   Whenever possible, molecular sequencing of a viral isolate from a case thought to be vaccine-related should be attempted.

7. The definition of a false positive following measles/rubella IgM serological testing is complex. There may be situations where a definitive answer cannot be reached, and situations need to be considered on a case-by-case basis taking into account clinical and epidemiological data and laboratory results. With the exception of pregnant women in an outbreak, false positive results are only really an issue for sporadic cases.

   PAHO should work to develop a guideline for defining testing protocols for measles/rubella; this would include recommended kits, algorithms for testing, and the various scenarios for false-positive IgM results.

   In the meantime, a sensible approach for follow-up of IgM results thought to be positive is for the reference laboratory to repeat the IgM test with the same kit and to test the sample with an alternative IgM assay, as well as to perform other types of

confirmatory tests such as IgG serology on paired sera and avidity assays, and do viral isolation/detection when possible.

Consideration should be given to establishing a group of national experts which meet regularly to review cases that are difficult to classify or have laboratory results difficult to interpret.

8. Depending on the diseases circulating in a country, the appropriate kits for IgM detection must be available, such as for dengue and for parvovirus B19. Where dengue is endemic, dengue testing is a very important component of the laboratory investigation of suspected rubella cases since it has been shown that IgM false positives can occur with particular kits.

9. In pregnant woman who had a serum sample collected within 5 days of illness onset, a second serum samples for rubella-specific IgM testing is recommended regardless of whether the initial result was positive or negative. Additionally, the important clinical management decisions regarding rubella in pregnant women require that multiple approaches to laboratory confirmation be used. These approaches can include, but are not limited to, IgG serology (seroconversion or a >4 fold rise in titer) and viral isolation/detection.

   The other situations in the investigation of sporadic rubella-suspect cases for which a second serum sample is useful still need to be outlined.

10. Like with polio, the monitoring of national laboratory should generally include the surveillance system, and not only focus on the laboratory techniques. Therefore, regular visits with epidemiologists of the EPI program (including the national Ministry of Health as well as the PAHO/WHO Representation) are important to promote coordination and exchange of information.

    There is a need for improved coordination between laboratory and epidemiology personnel, continued education of laboratory personnel, and the required availability of IgM kits provided by PAHO.

    For measles and rubella IgM quality assurance, 10% of negative samples, all positives, and all equivocal results need to be submitted to the national or regional reference laboratory. Proficiency testing should be done annually by both the national (from PAHO in collaboration with CDC) and sub-national (from the national laboratories) laboratories.

ANNEX 3

MEETING OF THE POLIO LABORATORY NETWORK
2 November 2004, Mexico City

The global polio laboratory network must continue to be fully functional until a global certification of polio eradication, currently estimated to occur in 2010-2012. This time frame recognizes that surveillance of wild viruses needs to continue for at least three years after the last isolation of wild poliovirus. Surveillance for vaccine-derived polioviruses (VDPVs) needs to continue for a similar period after OPV cessation. Beyond this period, some still undefined laboratory support will be needed in case of poliovirus re-emergence or bioterrorism.

In the Region of the Americas, following the declaration of polio-free status in 1994, AFP surveillance and polio identification in the laboratories have been maintained at levels that generally meet global standards. However, the lack of an adequate process of accreditation and documentation of laboratory performance does not allow laboratories, PAHO and WHO/HQ to document laboratory proficiency systematically, to detect deviations or deficiencies in performance, and to take appropriate corrective action.

Recommendations:

1. PAHO Polio Laboratory Network Management and Support:

- The links of PAHO laboratories with the global polio laboratory network should be strengthened to assure access to WHO weekly reports, current technical documents and other relevant publications. This information will be used to improve surveillance of possible importation of wild polioviruses from endemic countries or the emergence of circulating VDPVs.

- To assure effective management, improvements should be made within the PAHO network to improve the process of performance monitoring. Regular communication on laboratory data and performance issues should be established between the laboratories of the Region, the Institutions/Ministries of Health, PAHO, and WHO/ HQ.

- To accomplish the previous recommendations, the appointment of a regional laboratory coordinator should be expedited.

2. Laboratory Accreditation:

- To update information about laboratories in the Americas and share this data with WHO/HQ, accreditation checklists will be distributed by the Global Polio Laboratory

Coordinator to be completed by laboratories and returned within one month of receipt. The forms, covering performance in the 12 months prior to 30 September 2004, will be reviewed with the assistance of WHO/HQ and reports will be sent to laboratories within three months and will be linked with a plan of action to address any deficiencies identified.

- Results and feedback from the 2004 polio isolation and intratypic differentiation (ITD) proficiency tests will be sent to laboratories by PAHO. These results will contribute to assessment of laboratory performance.

- Only two laboratories in the Region are currently accredited by WHO as ITD laboratories, Fiocruz (Brazil) and CDC (USA). Poliovirus isolates should be sent to one of these two laboratories for characterization within 7 days of detection following global requirements.

- For the program to use ITD results from other laboratories in the network, priority should be given to formal accreditation of appropriate laboratories. The cost effectiveness and resource implications of accrediting new laboratories for ITD within the Region should be evaluated by PAHO in consultation with WHO/HQ. Decisions are needed about accrediting 2-3 additional laboratories to do ITD tests.

3. Quality Assurance:

- The above accreditation and management activities will be used to help identify the major obstacles to high-quality laboratory performance. The existing system should be refined to assure the rapid reporting of polio laboratory data, including all critical laboratory performance indicators to provide appropriate feedback on a continuous basis and effective regional and global monitoring of laboratory performance.

- Internal quality assurance (QA) with an aim to rapidly detect and correct possible performance deficiencies should be an integral part of daily laboratory activity. Assessment of QA programs for laboratory procedures will be emphasized as part of the current accreditation process to assure appropriate implementation within the regional laboratories.

- Laboratories should complete implementation of cell sensitivity testing as part of the routine internal quality control program and complete performance of three valid tests of NIBSC and LQC reference standards in parallel as soon as possible.

4. Communication and Data Management:

- Reporting is an essential aspect of the quality control of laboratory work and of maintaining satisfactory records of laboratory results and activities. PAHO should provide a standardized format for data sharing which should include the information

required, the frequency of reporting, the appropriate recipients, and feedback to the laboratory/institution. A pilot computerized system with these capabilities for data management and reporting should be implemented in two laboratories and reviewed before the next laboratory meeting.

5. Future of the Polio Laboratories:

- Maintenance of polio laboratory activities in the future will require advocacy with partners and governments to assure continued support for surveillance activities that are a part of the WHO Strategic Plan.

- Within the Region, many laboratories and institutions continue to expand their technical capabilities to perform ITD and/or viral nucleic acid sequencing. To enhance the rapid detection of poliovirus as part of response strategies during the period of OPV cessation, or when shipment of polio isolates is less cost-effective, accreditation requirements for sequencing activities should be formulated before the next global laboratory network meeting.

- As wild poliovirus transmission will be interrupted in the near future, network laboratories are encouraged to set an example by implementing containment requirements of virus holdings. Laboratories should be encouraged to destroy all non-needed wild poliovirus materials.