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VACCINES AND IMMUNIZATION

The following report updates the Executive Committee on Member States' progress in the areas of vaccines and immunization, and on PAHO's role in supporting country efforts in building national immunization programs. A special acknowledgement is made of partners' sustained support to realizing immunization goals in the Americas.

By mid 2002, Venezuela is the only remaining country with endemic measles transmission. Member States are alerted on the factors that contributed to the outbreak in Venezuela. Surveillance for acute flaccid paralysis has been strengthened, in response to the Sabin 1 vaccine-derived polio outbreak in the Hispaniola between 2000-2001. Ongoing vaccination strategies to accelerate the control of rubella and prevent the occurrence of congenital rubella syndrome (CRS) have been successful. The re-urbanization of yellow fever continues to be a major concern.

The establishment of a surveillance infrastructure capable of generating relevant data on new vaccines remains an important collaboration of PAHO and Member States. Advances are also being made in promoting safe immunization, and on the changes being carried out by vaccine-producing countries to remain competitive. In lieu of the September 11, terrorist attacks and the potential threat of the deliberate use of smallpox virus as a biological weapon, PAHO convened two technical consultation meetings.

This document is presented for the consideration of the Executive Committee with the following objectives: (a) to request that Member States provide adequate financing and human resources to ensure that national and regional immunization goals are attained, including the implementation of timely and sensitive surveillance for detecting all vaccine-preventable diseases, (b) in order to reach the goal of interruption of indigenous measles transmission in the Western Hemisphere, to ensure that measles vaccination coverage of at least 95% is obtained in all municipalities of a country, coupled with the timely implementation of measles *follow-up* vaccination campaigns, to prevent the occurrence of explosive outbreaks due to importations; (c) to maintain the eradication of poliomyelitis in the Americas by sustaining high levels of vaccination coverage with oral polio vaccine; (d) to implement accelerated programs for the control of rubella and the prevention of CRS; (e) to prevent the re-urbanization of yellow fever through high levels of vaccine coverage in high risk areas; (f) to prepare for the introduction of new vaccines; and (g) to continue using vaccines of assured quality.

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1. Regional Advances in Immunization

This progress report on vaccines and immunization highlights the remarkable achievements of Member States in building national immunization programs and in establishing an infrastructure for local vaccine production and quality control of vaccines. Important breakthroughs in the Region in the fight against infectious diseases that can be prevented through vaccination have been attained in the 100 years of PAHO's existence, particularly in the last 25 years. These have served as a model for the development of global immunization initiatives.

The search for equity in immunization delivery has been at the forefront of PAHO collaboration with Member States, as has the need to strengthen the accountability of immunization programs to make effective use of available human and financial resources. Principal methods used by immunization programs in the Americas to improve service delivery have included periodic evaluation of national immunization programs; the elaboration of five-year and annual plans of action; the promotion of inter-agency coordinating committees; advocacy to promote the passage of immunization laws; and collaboration to identify localities with persistently low coverage levels, even within countries that report adequate aggregate national coverage.

Data from the year 2000 indicate that 84% of countries in the Americas had vaccination coverage for diphtheria, tetanus, and pertussis (DTP3) of over 80%, while only 52% of municipalities reported coverage for DTP3 of more than 95%. Much work remains to be done to achieve uniform coverage in all municipalities. Greater efforts are needed by Member States in targeting municipalities with low coverage with intensive vaccination activities, and in simultaneously improving the quality of vaccination data collected, analyzed, and reported. PAHO has recommended that all national immunization programs enhance the monitoring of vaccination activities by increasing supervisory visits at the local level, and by making use of a set of tools developed by the Organization to rapidly determine the quality of vaccination coverage.

PAHO partners, particularly the United States Agency for International Development (USAID), the Canadian International Development Agency (CIDA), the Centers for Disease Control and Prevention (CDC) of the United States of America, the Government of Spain, the March of Dimes, and the World Bank, have sustained their support to national immunization programs. Nurturing these partnerships, as well as those with the private medical sector, remains a critical strategy.

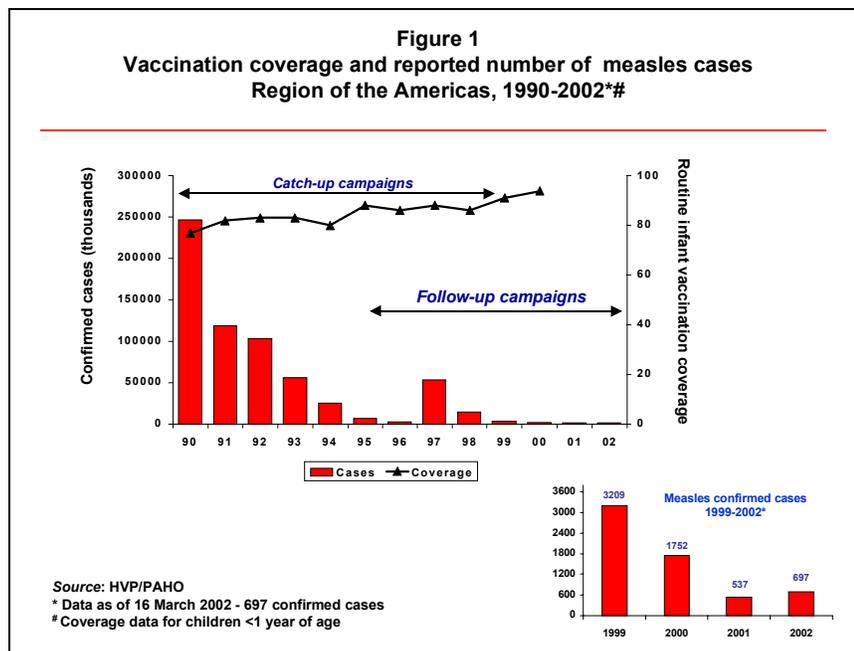
The global partnership formed in 1999 with the establishment of the Global Alliance for Vaccines and Immunization (GAVI) has brought together the public and private sectors, including national governments, the World Health Organization (WHO), the World Bank, the United Nations Children's Fund (UNICEF), the Bill and Melinda Gates Foundation, the Rockefeller Foundation, and the vaccine industry. GAVI and a parallel Global Fund for Vaccines have been supporting the procurement of vaccines against hepatitis B, Haemophilus influenzae type B (Hib), and yellow fever, as well as related safe injection equipment for countries with a gross domestic product per capita equal to or less than US \$1,000, and a population of fewer than 150 million. Only six countries in the Americas are eligible to apply for support from the Global Fund for Vaccines: Bolivia, Cuba, Guyana, Haiti, Honduras, and Nicaragua.

Careful coordination has been required between PAHO and the Global Fund for Vaccines to avoid duplication of work and implementation of parallel strategies and initiatives, and in the collection of data by the Fund on vaccine-preventable diseases in the Americas. GAVI objectives may conflict with PAHO's policy of fostering the use of national resources to pay for vaccines, since it can establish a precedent of external support for the procurement of basic inputs for national immunization programs.

2. Disease Control Initiatives

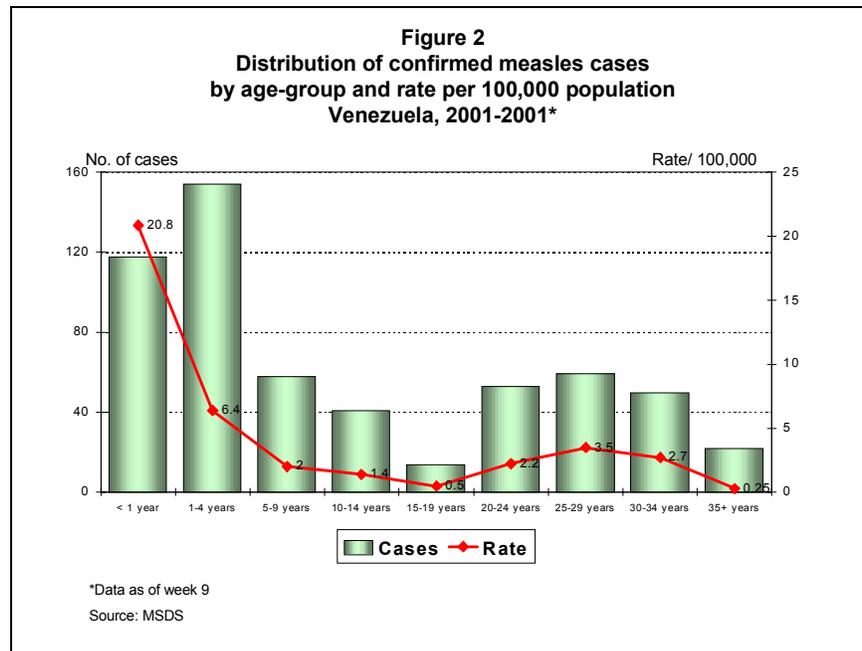
2.1 *Progress toward Measles Eradication*

Considerable progress is being made in the Americas in reaching the goal of interrupting indigenous measles transmission (Figure 1). Member States have intensified vaccination efforts, as well as surveillance activities and active searches for cases in health centers, schools, and high-risk communities. During 2001, endemic measles transmission occurred in only three countries in the Western Hemisphere: the Dominican Republic, Haiti, and Venezuela.



A total of 537 confirmed measles cases were reported in the Americas in 2001, with measles virus circulation reported in the Dominican Republic, Haiti, and Venezuela. This represents a 99% decrease from the approximately 250,000 measles cases reported in 1990. The Dominican Republic's last confirmed measles case occurred in June 2001, and Haiti's last reported case occurred in September 2001. In 2002, Venezuela is the only country where endemic measles transmission is prevalent. This country has been affected by a measles outbreak since August 2001, following an importation from Europe. As of mid-March 2002, a total of 687 confirmed measles cases and one death had been reported. Most cases have been in unvaccinated populations. Highest rates of infection are in the under-five age group, followed by young adults (Figure 2). Affected adult population groups include migrant workers, students, and health care workers. The outbreak in Venezuela has taken place in 28 municipalities in six of the country's 23 states. The state hardest-hit is Zulia, which is the most populated and borders Colombia. As of mid-March 2002, Colombia had reported eight confirmed measles cases, all due to importations from Venezuela. Endemic transmission of measles virus has not been detected in Colombia.

The re-emergence of measles transmission in Venezuela can be traced to the country's persistently low vaccination coverage levels achieved through routine immunization services in several areas. Between 1995 and 1997, routine vaccination coverage for one-year-olds was below 70%, in 1999 it increased to 80%, and in 2000 to 84%.



Annual routine coverage in parishes and municipalities currently affected by the epidemic has ranged from 10% to 30%. Experience gained in Venezuela and throughout the Americas in the past six years has highlighted the need to improve and strengthen supervision at the local level, including validating measles vaccination coverage through house-to-house monitoring, and validating surveillance information through active case finding. The outbreaks that have affected the Americas have also brought to light the important role susceptible young adults play in introducing the disease, and in its transmission.

The Americas continues to be under constant threat of importation of measles virus from other regions where the disease remains endemic. Measles importation has been responsible for outbreaks in Argentina, Bolivia, and the Dominican Republic in 1998-1999, in Haiti in 2000-2001, and in Venezuela in 2001-2002. Measles importations are unavoidable; therefore, the main strategy to prevent the re-initiation of endemic measles transmission is to maintain the highest population immunity possible. Member States need to maintain high routine vaccination coverage of children in all localities and carry out special vaccination efforts targeting adolescents and young adults who are at highest risk of being exposed to measles virus, including health care workers.

2.2 Maintenance of Poliomyelitis Eradication

Important efforts have been undertaken by Member States following the Sabin type 1-derived poliovirus outbreak in Hispaniola in 2000-2001. The first cases of poliomyelitis due to vaccine-derived poliovirus type 1 were reported in October 2000 in the Dominican Republic. A total of 13 and 8 cases have been confirmed in the Dominican Republic and Haiti, respectively. All cases were among individuals either inadequately vaccinated or unvaccinated. The outbreak was the result of prolonged circulation of vaccine-derived poliovirus in areas with very low vaccination coverage with oral polio vaccine (OPV), as well as poor sanitation conditions. This allowed OPV-derived viruses to establish circulation. Intensified national vaccination efforts in both countries, coupled with surveillance and active search for suspected cases, have prevented further spread of this mutant virus. The last reported cases of poliomyelitis due to vaccine-derived poliovirus were in January 2001 in the Dominican Republic, and in July 2001 in Haiti.

Noteworthy has been the political and financial commitment shown by health authorities and health workers alike in the Dominican Republic and Haiti, as well as the strong support of the international community, particularly the Government of Canada, USAID, Rotary International, CDC, and the World Bank. This joint collaboration has offered an excellent example to the world of effective interagency coordination, both in technical and financial areas, in reaching a critical objective.

In response to the vaccine-derived outbreak in 2000-2001, it was recommended that countries undertake an evaluation of the risk of failing to detect poliovirus circulation, based on the performance of national surveillance systems in the last five years, and the level of vaccination coverage with OPV reached during those same years. This exercise has highlighted the need to perform evaluations at the local level in order to see variations within countries (Table 1).

Table 1. The Americas, 1996-2001

Country	Rate of Acute Flaccid Paralysis with Adequate Sample Per 100,000 < 15 Years Old						Oral Polio Vaccine 3 National Coverage % in Children <1 Year Old					
	1996	1997	1998	1999	2000	2001	1996	1997	1998	1999	2000	2001
Argentina												...
Bolivia												
Brazil												
Canada										
Caribbean*												
Chile												
Colombia												
Costa Rica												
Cuba												
Dom. Rep.												
Ecuador												
El Salvador												
Guatemala												
Haiti									
Honduras												
Mexico												
Nicaragua												
Panama												
Paraguay												
Peru												
Uruguay												...
USA
Venezuela												...

 ≥ 0.8
  < 0.8
  $\geq 80\%$
  $< 80\%$

..... Data not available Source: country reports/PSS * English-speaking

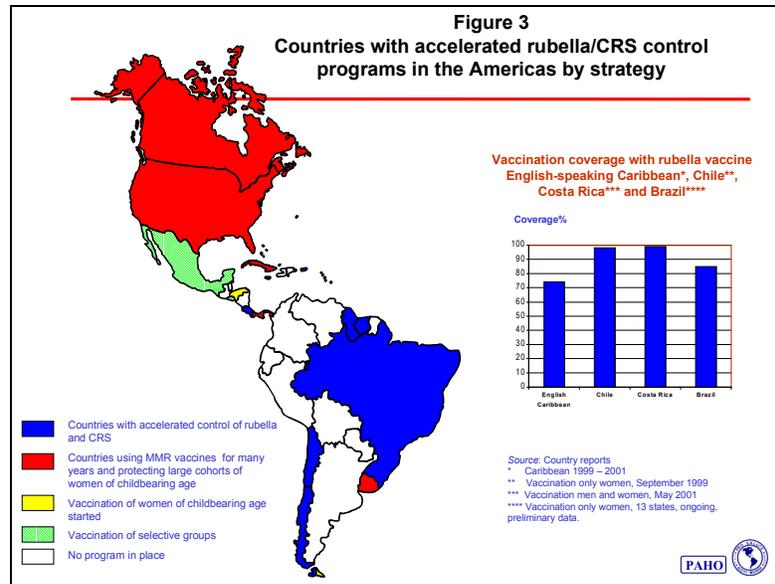
As part of the certification process for global poliomyelitis eradication, 13 out of the 35 countries in the Americas have established national commissions for the containment of wild poliovirus in laboratories. This is a requirement that countries need to fulfill before they are certified as free of poliomyelitis. Given the risk associated with wild poliovirus contamination to the environment, those Member States that have yet to establish a national commission are encouraged to do so. Member States are also asked to sustain high levels of OPV coverage and active surveillance in all areas of a country, and to support financially the work being done by the laboratories that comprise the Polio Laboratory Network in the Region.

2.3 Rubella

Of the 44 countries and territories in the Western Hemisphere, 40 have introduced routine childhood rubella programs, and several have embarked on the accelerated control of rubella and prevention of congenital rubella syndrome (CRS). These initiatives are providing useful knowledge and experience regarding the use of adequate vaccination strategies, as well as lessons learned in mass vaccination of adult populations, which will greatly aid in the implementation of similar campaigns in the Region and worldwide.

The principal goal of a rubella control strategy in the Americas is to prevent the occurrence of CRS. Most countries in the Region have already implemented routine childhood rubella vaccination, and this schedule is protecting children as they reach their first year of life. Nevertheless, this vaccination strategy will likely take over 20 years to control CRS, as several cohorts of childbearing women will remain susceptible to rubella virus. Therefore, PAHO has been actively engaged during the past two years in supporting country efforts to accelerate the control of rubella through the implementation of a one-time adult mass vaccination campaign. This strategy would achieve a more rapid decrease of rubella cases and of infants born with CRS. An accelerated rubella control strategy would also prevent the occurrence of the approximately 20,000 CRS cases per year in the Americas, as well result in substantial savings from disability costs associated with this severe condition.

Of the 40 countries and territories that have already introduced rubella vaccine in their routine schedule, 12 countries and 6 territories in the English-speaking Caribbean and 3 countries in Latin America have conducted accelerated rubella control programs that include adults. The English-speaking Caribbean goal for elimination of CRS is well under way, and both Cuba and Uruguay have successfully eliminated rubella and CRS. Brazil and Chile have conducted rubella campaigns targeting adult women for the prevention of CRS, and Costa Rica carried out a mass campaign for the control of rubella and prevention of CRS, targeting both men and women between the ages of 15 and 39 (Figure 3).



As a result of the integration of the surveillance systems for rubella and measles, there have been improvements in the sensitivity and specificity of rubella diagnosis. There is underreporting, however, and the true magnitude of the rubella disease burden remains unknown. CRS surveillance in the Americas is also still at an infancy stage.

Important steps have been taken by countries in seeking active participation of the private medical sector, such as the work being done with the Regional Federation of Obstetrics and Gynecology. Progress continues to be made, in collaboration with PAHO's Latin American Center for Perinatology and the Collaborative Latin American Study Project of Congenital Malformations, in the use of a standard case definition for CRS in the Region. Member States will need to strengthen rubella and CRS surveillance. Efforts are also needed to improve the investigation and documentation of outbreaks and follow-up procedures of pregnant women infected with rubella virus, and to expand the capabilities of virus isolation in national laboratories.

2.4 *Yellow Fever*

While cases of sylvatic yellow fever continue to occur in countries located within the enzootic area, a decrease in reported cases has been observed in the last four years as a result of intensive vaccination carried out in Bolivia and Brazil. The identification of outbreaks of the disease and virus circulation in 2001 in non-enzootic areas, coupled with known widespread distribution of *Aedes aegypti*, the urban vector of this disease, highlight the need for endemic countries to implement the preventive measures recommended by PAHO.

Member States are urged to continue strengthening surveillance of clinical cases compatible with yellow fever, in order to ensure the expeditious implementation of control measures. In support of enhanced sensitivity of yellow fever surveillance, at least one sentinel site should be established at the department or health area level for the surveillance of fever and rash syndrome. Regarding vaccination strategies, the entire population should be immunized against yellow fever in municipalities within enzootic areas, and in areas with housing showing a level of infestation by *Aedes aegypti* greater than 5%. The incorporation of yellow fever vaccine in the routine schedule for children, as well as vaccination of all travelers entering enzootic areas, should be mandatory. Member States are requested to maintain an adequate supply of vaccines to respond in a timely manner to outbreaks. The implementation of an integrated vector control and surveillance program will maintain a low density of *Aedes aegypti* in urban areas, and will also greatly aid in the prevention of outbreaks caused by dengue virus that are affecting the Region.

2.5 Neonatal Tetanus

The incidence of neonatal tetanus (NNT) continues its downward trend in the Region. The reported number of cases was 120 in the year 2000. The disease is now confined to less than 1% of all districts in the Americas. Epidemiological characteristics continue to show that cases occur predominantly among rural infants of multiparous women, who at times lack prenatal care, are unvaccinated, and have for the most part delivered at home.

PAHO is making a special appeal to all Member States to finish the task of NTT elimination, by emphasizing the epidemiological and social conditions associated with the remaining cases, such as migration, marginality, and incidence in remote areas. Special emphasis should be placed on missed opportunities of vaccination by making efforts to vaccinate every pregnant woman or woman of childbearing age at each contact with a health facility.

3. Vaccine Introduction

Major attention remains on the introduction of new and/or combined vaccines in the routine immunization schedule, particularly those that have already been available on the market for the past 15 years in the developed countries. These include the measles-mumps-rubella (MMR) vaccine, the hepatitis B vaccine, and newer vaccines such as Hib and combination vaccines. The availability and use of combination vaccines, such as DTP+Hib, DTP+HB, and DTP/HB+Hib, have simplified the administration of vaccine antigens against major childhood diseases, resulting in fewer injections for infants and children, as well as fewer visits to health centers, which increases compliance and coverage.

Support has continued in the establishment of networks of sentinel hospitals, linked to public health laboratories and epidemiological units of the ministries of health, to monitor bacterial pneumonia and meningitis, specifically those due to *S. pneumoniae*, *H. influenzae* and *N. meningitidis*. This system is providing information on prevalent pneumococcal serotypes responsible for invasive diseases in children and their antimicrobial susceptibility patterns; on the impact of vaccination on Hib diseases; and, soon, on the status of meningococcal serogroups responsible for diseases in the Region. The information generated is validated by a quality control system that operates through three subregional centers (in Brazil, Colombia, and Mexico), which is connected to the National Center for Streptococcus in Alberta, Canada (for *S. pneumoniae* reference), and the Haemophilus Reference Unit for the Public Health Laboratory Service in the United Kingdom. More recently, surveillance has been improved in order to establish a bridge with ongoing clinical trials of pneumococcal vaccines that are using chest X-ray interpretation as the confirmatory criteria for a bacterial pneumonia. By integrating the information generated from the surveillance system with the results from trials, more precise information on the possible impact of the pneumococcal vaccine in each country will be available. Cost-effectiveness studies are being conducted in Brazil, Chile, and Uruguay, which will generate comparative costs for different interventions. This critical information will be made available to decision-makers.

A similar approach is being followed for rotavirus vaccines. The same network of sentinel hospitals will be involved in monitoring rotavirus diseases, thereby strengthening hospital laboratory and diagnostic capabilities.

4. Safe and Quality Immunization

PAHO continues to place high priority on establishing and strengthening mechanisms that will allow countries to guarantee the utilization of quality vaccines. A vaccine of quality is defined as one that has been produced according to Good Manufacturing Practices (GMP) and complies with all the specifications and requirements set by international standards. The quality can be assured only if the National Regulatory Authority (NRA) of the country where the vaccine is produced complies with all six basic regulatory functions, which include: (a) licensure of all vaccines used; (b) clinical evaluation of vaccines; (c) release of every vaccine lot to be used; (d) access to a laboratory that can perform vaccine testing; (e) compliance with GMP; and (f) implementation of a post-marketing surveillance system.

PAHO collaboration with Member States is geared toward strengthening the NRAs in the Region and assuring compliance with the six functions of vaccine-producing countries, while concentrating on licensing and lot release of vaccines, as well as post-marketing surveillance in the non-producing countries. In support of this strategy, training is being developed and carried out in vaccine licensing, lot release, and GMP.

With globalization and the creation of subregional free trade agreements, the harmonization of regulatory activities has become critical. PAHO has collaborated with NRAs to harmonize licensing procedures of vaccines. Furthermore, professionals of regional NRAs have been selected since 1999 to spend three to four months at PAHO headquarters learning and assisting in the Organization's activities in quality control. To date, professionals from Argentina, Brazil, Chile, Colombia, Cuba, and Venezuela have participated.

In the area of quality control testing of vaccines, PAHO is working with National Control Laboratories (NCLs) to achieve higher levels of proficiency and qualification for the establishment of regional laboratory capacity for specific vaccine testing, in support of NRAs in the Region and of the PAHO Revolving Fund.

Recognition by local vaccine manufacturers of the need to make the appropriate investments to upgrade their facilities, equipment, and procedures to comply with GMP and national/international requirements remains of key importance. Technical and economic feasibility studies are being undertaken to identify institutional strengths, weaknesses, and needs for improvement. A major breakthrough has been the certification by the WHO assessment system of two vaccine manufacturers in the Region, Biomanguinhos in Brazil and the Centro de Ingeniería Genética y Biotecnología in Cuba, for yellow fever vaccine and hepatitis B vaccine. Both producers are now suppliers to United Nations agencies.

Some local producers have entered into joint ventures with major vaccine manufacturers for specific vaccines of regional interest. Examples of such associations are Biomanguinhos and Glaxo SmithKline for the production of Hib vaccine, Instituto Butantán (Brazil) and Aventis Pasteur for influenza vaccine, and the Instituto Finlay (Cuba) and Glaxo SmithKline for meningococcal group B vaccine. The possibility of joint ventures for vaccine production among Latin American manufacturers is being explored by PAHO.

Regarding safe immunization, information is being disseminated on an ongoing basis to familiarize health workers with procedures to effectively handle public concerns about the safety of vaccines, as well as for dealing with events that might be attributed to immunization, and measures that will lead to a reduced number of adverse events during campaigns. The critical role played by the mass media in this regard has been included as a topic in PAHO's annual subregional meetings with the managers of immunization programs of the Southern Cone, the Andes, Central America, and Brazil. A key message has been the need to forge alliances with the mass media.

The number of countries using safety boxes and those ensuring the proper disposal of syringes and needles is increasing. These measures have guaranteed the safety of health workers and that of the community. Health authorities in Member States need to continue advocating and supporting injection safety practices. Critical aspects are training

and efforts to investigate reported events immediately. These steps will ensure that the public's trust in national immunization programs is maintained.

5. Smallpox

Following the September 2001, terrorist attacks in the United States, there was heightened awareness of the potential threat of deliberate use of smallpox virus as a biological weapon against civilian populations. It was deemed that existing low immunity levels of the population due to cessation of smallpox vaccination over 20 years ago, coupled with increased movement, could allow the disease to spread rapidly, if no response were put in place in a timely manner.

In response to Member States' concerns, PAHO convened two technical consultation meetings to examine current and future challenges, and the potential for regional production of quality smallpox vaccines to cope with emergency situations. There was discussion of the need to develop a coordinated response effort, and to include a strategic reserve of vaccines at the regional level and to create an enhanced public health infrastructure. Recommendations were made for Member States to review their surveillance and diagnostic capabilities for rapid case detection and investigation of smallpox, and to strengthen emergency preparedness at hospitals to deal with mass casualties.

Regarding the potential for production of quality smallpox vaccines in the Americas to cope with emergency situations, it was noted that the production of smallpox vaccines would be a sporadic and/or transitory activity. Member States needed to carefully assess replacing or delaying current production of vaccines of public health importance. Furthermore, the majority of vaccine-producing countries in the Americas would have to improve their installed capacity to absorb immediate smallpox vaccine production.

During the meetings, it was agreed that PAHO would provide information and training to strengthen Member States' surveillance infrastructure; that the PAHO Laboratory Network for Measles/Rubella (fever and rash) would be equipped both technically and with reagents to diagnose smallpox; and that the Organization would offer technical cooperation and facilitation of seed lots and other materials, in case any given country decided to go into production, provided that the National Control Authority met the six basic criteria established by WHO. It was further stressed that consensus needed to be reached among Member States that one case of smallpox in any country was a threat to the entire Region and, therefore, countries that produce and/or have stocks of smallpox vaccine would make it available to control the outbreak in the affected country.