

PAHO/IM/2003-00005
ORIGINAL: Spanish



**Pan American Health Organization
World Health Organization**

**Family and Community Health Area
Immunization Unit**

***Regional Meeting on the Implementation of
Rotavirus Epidemiological Surveillance***

Generating Information for Decision-making

Final Report

Lima, Peru

4-5 September 2003

INTRODUCTION

The Regional Meeting on the Implementation of Rotavirus Epidemiological Surveillance was held in Lima, Peru, on 5-6 September 2003. The meeting was opened by the Minister of Health of Peru, Dr. Álvaro Vidal. Also in attendance were Dr. Luis Eliseo Velásquez, Representative a.i. of PAHO/WHO in Peru, Dr. Gina Tambini, Manager of the PAHO Family and Community Health Area; Dr. Duncan Steele from the WHO/Geneva Representative Office; Dr. Ciro A. De Quadros, representing the Albert Sabin Institute; Dr. Julie Jacobson, representing the Children's Vaccine Program (CVP); Dr. Joe Bresee, representing the Rotavirus Vaccine Program (RVP); and Dr. Jon Andrus, Chief a.i. of the PAHO Immunization Unit.

The meeting brought together professors and researchers from a number of countries of the Americas; representatives of CDC, Emory University, and the pharmaceutical industry; managers of EPI and epidemiological surveillance programs in Brazil and the Andean and Southern Cone subregions; and staff members of the PAHO Immunization Unit.

Dr. Ciro A. De Quadros chaired the meeting and Dr. Jon Andrus acted as secretary.

Dr. Carlos Castillo-Solórzano introduced the subject of the meeting and presented its objectives.

OBJECTIVES OF THE MEETING

- Share knowledge about rotavirus, progress in the development of new vaccines, experiences with surveillance, and information about on the work being carried out in the Region with managers of EPI and Ministry of Health surveillance.
- Develop in-depth knowledge about rotavirus epidemiology in the countries of the Region.
- Discuss issues shared in common by the surveillance projects to be undertaken in the Region in order to determine the disease burden, based on the WHO Generic Protocol.
- Develop strategies to support evaluation of the safety and efficacy of the new rotavirus vaccines in the Region.
- Review the process of member participation, coordination, and support.

GENERAL ISSUES IN ROTAVIRUS SURVEILLANCE

Rotavirus Epidemiology and Disease Burden: Global and Regional Estimates

Rotavirus (RV) is a major cause of diarrhea throughout the world. It is a democratic disease that affects all, both rich and poor. But fortunately it is a vaccine-preventable disease.

The virus was discovered 30 years ago. It consists of 11 double-stranded RNA segments encased in a bilayered capsid containing three viral proteins (VP). These proteins, which are infective and induce an immune response in the host, are the basis of the classification system used today: VP6 determines the group and subgroup, while VP4 is indicative of type P, and VP7 is associated with serogroup G. The variations in these viral proteins have an impact on immunity, the methods used for detection, and effective vaccine development.

RV infection can range from an asymptomatic state to severe diarrhea. The virus destroys the normal architecture of the intestinal microvilli, which explains why this infection is associated with dehydration. Children will often have several RV infections because the first infection, which is usually the most severe, does not provide complete protection against subsequent infections, although it does confer some protection against severe disease.

RV mainly affects children under 5 years of age, causing diarrhea and sudden vomiting accompanied by fever in 30%-50% of the cases, following an incubation period of about two days. During the infection, even if it is asymptomatic, the virus is shed in feces at levels of 100 billion viral particles per mL. Since only about 10,000 to 10 million particles can cause clinical disease, it is easy to see that the principal mode of transmission is the fecal-oral route. Other transmission mechanisms are also suspected.

RV is the most frequent cause of severe gastroenteritis in both the developing and developed countries. However, the epidemiology of the two situations differs. In developing countries, children acquire the infection earlier in life; infections seem to occur throughout the year; and they appear to be caused by a greater diversity of strains than are found in the developed countries. Moreover, coinfection and comorbidity are common in developing countries, contributing to the higher mortality observed.

In terms of the events associated with severe RV disease, including both hospitalization and death, RV affects rich and poor countries alike. Although many good studies have been conducted at the world level and in Latin America, few them have been carried out long enough to control for any stationary effects and thus provide comparable results. However, based on the data in hand, a correlation can be seen between the economic level of a country and the number of hospitalizations and deaths from rotavirus.

Taking this correlation into account, as well as using published data on proportions of rotavirus in diarrhea cases, a CDC team headed by Umesh Parashar updated the estimates of disease burden at the world level. The findings are presented both as a child's risk of having a rotavirus-related event before the age of 5 and as the total number of events in the world. The risk of having a rotavirus infection is 1:1; that of having to seek consultation, 1:5; that of being

hospitalized, 1:65; and that of dying, 1:293. For the world as a whole, this means 111 million cases of rotavirus-related diarrhea, 25 million consultations, 2 million hospitalizations, and 440,000 deaths, with 82% of the deaths taking place in developing countries.

If the same methods of estimating disease burden are applied to the American Region, RV is the cause of approximately 75,000 hospitalizations and 15,282 deaths. These numbers are only estimates.

Rotavirus disease is one of the most important causes of diarrhea-related morbidity and mortality in the world. According to data from the studies conducted to date in Latin America, it is also a very important disease in our countries; however, there is need for more high-quality data on the disease, standardized for comparability, as well as for studies on the disease burden in the Region, so that each country can take the most appropriate steps to prevent it and be in a position to decide on introduction of a vaccine when it becomes available.

The Economic Cost of Rotavirus Disease

The economic aspects of RV are important because of the burden it imposes in terms of morbidity, mortality in children, and cost to health systems, families, and society in general.

There are two types of economic analyses:

1. Economic impact, in which the social cost is calculated on the basis of epidemiological data and event costs which make it possible to estimate the cost for cohorts in a given year, the cost for families, and the burden on the health system.
2. Economic evaluation of cost-effectiveness in terms of the value of the health intervention, which is obtained by combining the cost of vaccination and the resulting health benefits for health. Cost-benefit compares the economic investment and the economic benefit.

Economic Impact

There are three broad types of costs:

- Direct medical cost associated with medical care, hospitalization, consultation, diagnostic tests, and treatment (paid by the health system and the family).
- Other direct expenses, such as those incurred by the family in connection with hospital visits or in addition to medical costs, including transportation.
- Indirect costs, expressed in terms of lost production by society in general as a result of labor absenteeism.

In order to estimate national impact, information is needed on the rate of hospitalizations and outpatient visits, as well as on the average cost of each type of event.

How to Evaluate a Vaccine

The impact and cost of vaccination can be estimated on the basis of information regarding expected coverage; effect on the prevention of hospitalization, outpatient visits, and mortality; and cost of administration.

The benefit for a national vaccination program and a health system should be considered relative to the cost saved as a result of vaccination. For purposes of decision-making in the different countries, limitations on resources should be taken into account. This means that it is necessary to have reliable information that will show whether or not the intervention is worthwhile and a good investment – i.e., whether the medical cost saved is greater than the amount being spent; whether the total cost to society plus the costs prevented are greater than those of the vaccination program; and comparisons for specific interventions.

If the cost of vaccination is less than that of the costs avoided, the economic value would be very high, but most health interventions do not reach this goal. If the cost of vaccination is greater than the cost avoided (i.e., if vaccination entails a net investment), it may still be a good investment in health. In cost-effectiveness studies, the use of a rotavirus vaccine can be compared with other health investments in order to prioritize the allocation of resources.

Rotavirus Laboratory Surveillance

The development of vaccines against severe rotavirus diarrhea is based in part on the notion that homotypic and heterotypic protection is generated either against a common G serotype (monovalent vaccines) or against multiple serotypes (multivalent vaccines).

For this reason, the characterization of the most common G and P serotypes, so that they can be considered for inclusion in vaccines, is a high priority for surveillance. By the same token, after the introduction of vaccines, it is essential to monitor the circulating strains in order to see if the vaccines are effective against all the serotypes and also if the vaccine strains have become intermixed with wild human rotavirus.

The pattern methods of characterization, such as reverse transcriptase polymerase chain reaction (RT-PCR) for genotyping and monoclonal antibodies for serotyping, identify more than 95% of the circulating strains of rotavirus. However, some strains cannot be characterized using the proposed methods because of the presence of new, unfamiliar strains and genetic and antigenic variants of some of the serotypes. Hence molecular nucleotide sequencing methods and traditional virologic methods, such as neutralization with specific antisera, need to be used for the characterization of these strains.

DEVELOPMENT OF A ROTAVIRUS VACCINE

GlaxoSmithKline Human Rotavirus Vaccine

Below is a summary of clinical development of the vaccine in Latin America planned for the period 2003-2005:

Studies have been focused on the preliminary characterization of vaccines in order to understand the following:

- The effect of HRV vaccine on the immunogenicity of oral polio vaccine (OPV);
- Excretion of vaccine rotavirus;
- Communicability of the rotavirus excreted;
- Genetic stability of the vaccine viruses.

At the same time, steps are being taken toward implementing a phase III research plan for field-testing the vaccine and carrying out economic and epidemiologic studies.

The principal findings from these studies may be summarized as follows:

1. The OPV vaccine maintains its immunogenicity after administration of the rotavirus vaccine when there is an interval of at least two weeks between the two doses (Latin American study).
2. The impact of OPV vaccine on the efficacy of the rotavirus vaccine is being evaluated.
3. There is preliminary evidence of excretion and communicability of vaccine rotavirus after vaccination.
4. There is preliminary evidence suggesting that the excreted vaccine maintains its genetic stability.
5. Phase III studies have been conducted in Argentina, Chile, Colombia, Costa Rica, the Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela to determine the safety and efficacy of the vaccine.
6. Population-based and sentinel site studies aimed at understanding the epidemiology of the disease (incidence, age distribution, and seasonal occurrence) are being carried out in Argentina, Brazil, the Dominican Republic, and Mexico. Economic studies, to be conducted in Argentina, Brazil, Chile, the Dominican Republic, Honduras, Mexico, Panama, and Venezuela, are aimed at determining the number of events prevented (deaths, hospitalizations, and cases of severe diarrheal disease), as well as the costs avoided by type of cost and source of payment. Cost-benefit and cost-effectiveness analyses will take into account the events avoided, the cost of deaths prevented, and cost in terms of years of life saved or years of life saved adjusted for disability.

Merck & Co., Inc.

RotaTeq™¹ is a pentavalent rotavirus vaccine, containing 5 live human-bovine reassortant strains (designated G1, G2, G3, G4, and P1). The reassortant strains are based on a bovine WC3 (Wistar Calf 3) rotavirus backbone in which genes coding for surface proteins have been replaced by comparable genes from the indicated human rotavirus serotypes. RotaTeq™ is a liquid, buffer-stabilized formulation that is stored at 2 to 8°C. The vaccine is administered orally in a 3-dose regimen beginning at the age of 2 months with 1- to 2-month intervals between doses.

Several clinical studies to date suggest that Merck's rotavirus vaccine is generally well tolerated and efficacious against the rotavirus serotypes contained in the vaccine, which account for over 80% of rotavirus disease worldwide. In a double-blinded, placebo-controlled Phase IIa proof-of-concept study, the safety and efficacy of a quadrivalent (G1, G2, G3, and P1) vaccine was evaluated among 439 infants. The vaccine was approximately 75% efficacious against any rotavirus disease regardless of severity or serotype, and 100% efficacious against severe rotavirus disease. The vaccine was well tolerated, with no statistically significant increase in the incidence of fever, vomiting, diarrhea, or irritability among vaccine recipients as compared with placebo recipients during the 14 days after a dose.

As a result of the reported association of intussusception with another rotavirus vaccine, RotaShield® (Wyeth), a study to assess the risk of this rare serious adverse experience (SAE) with RotaTeq™ was initiated in 2001. This large-scale Phase III trial is referred to as REST (Rotavirus Efficacy and Safety Trial). This is a randomized, placebo-controlled trial designed to examine the safety of RotaTeq™ with respect to SAEs, particularly intussusception.

In the REST study, six to 12-week-old infants are enrolled to receive 3 doses of vaccine or placebo orally at 4 to 10 week intervals. They are actively followed for serious adverse experiences, including intussusception, for at least 42 days after each dose. A Safety Endpoint Adjudication Committee evaluates potential cases of intussusception as they occur. Potential cases that are positively adjudicated are reported to a Data and Safety Monitoring Board (DSMB) which unblinds the treatment arm of the cases and makes recommendations about continuing the study. Graphs of stopping boundaries have been provided to the DSMB to plot the vaccine and placebo cases occurring within 7 days and 42 days after any dose. The graphs incorporate a stopping boundary that was drawn based on a statistically significant increase in the incidence of intussusception among vaccine versus placebo recipients. If the stopping boundaries were to be reached at any point in the study and the DSMB deemed it clinically appropriate, the DSMB would recommend stopping the trial. To ultimately declare safety with respect to intussusception, 2 criteria must be met: 1) No increased risk of intussusception detected during interim safety monitoring and 2) a clinically acceptable ratio of intussusception cases among vaccine versus placebo recipients at the end of the study. The group sequential design of this study calls for an evaluation of the incidence of intussusception among vaccine and placebo recipients after 60,000 subjects have completed dosing and 42 days of follow-up after the last dose. If the second component of the statistical criteria for declaring safety is met, enrollment will be stopped. If the second component of the statistical criteria is not met, another

¹ RotaTeq is a trademark of Merck & Co., Inc., Whitehouse Station, N.J., U.S.A.

group of 10,000 subjects will be enrolled and the incidence of intussusception among vaccine versus placebo recipients re-evaluated after those subjects have completed dosing and follow-up.

REST is currently enrolling infants in 11 countries around the world, including several Latin-American countries. As of October 2, 2003, more than 57,000 infants have been enrolled and have received at least one dose of either vaccine or placebo.

The Development Team is blinded to the final adjudication decision (case versus non-case) and the treatment arm (vaccine versus placebo) of potential intussusception cases that have occurred in the study to date. Although several potential cases have occurred, the characteristics and timing of the potential cases with respect to vaccination suggest that these are background cases and not vaccine related. The incidence of potential cases observed is approximately 1/2500 to 1/3000 infant-years and this incidence is similar to the projected background rate of 1/2000 infant-years that was used for planning the study. No potential cases have been observed within 2 weeks after any dose.

In summary:

- In studies done to date, Merck's investigational pentavalent rotavirus vaccine has demonstrated ~100% efficacy against severe disease and ~70% efficacy against any rotavirus gastroenteritis.
- A large-scale trial, REST, is underway to evaluate the efficacy and safety of the final vaccine formulation, particularly with respect to intussusception
- Preliminary data from REST suggest that the final vaccine will be generally well tolerated
- REST has been designed to demonstrate that the risk of intussusception with vaccination is clinically acceptable.

EXPERIENCES IN ROTAVIRUS SURVEILLANCE

Regional Rotavirus Surveillance in Asia

Rotavirus surveillance got under way in Asia in 2001, after discussion of the protocols in 1999-2000 with the support of CVP, WHO, Merck, GlaxoSmithKline (GSK), and CDC. The goals for the surveillance network are to define the epidemiology and estimate the disease burden in the Region; describe the distribution of the strains; obtain data for decision-making regarding introduction of the vaccine; and develop a surveillance system that can be used for post-licensing evaluation of the impact of vaccination. The surveillance system consists of 36 sentinel hospitals in 9 countries (Korea, China, Taiwan, Hong-Kong, Viet Nam, Myanmar, Thailand, Malaysia and Indonesia), including both urban and rural areas, different socioeconomic levels, and tropical and temperate climates. A summary of the data is reported to CDC on a monthly basis. Several institutions are collaborating in the network, which also has the support of CVP, WHO, Merck, GSK, and CDC. The data collected between August 2001 and July 2002 show a rotavirus of detection rate of 45%, with variations ranging from 18% to 67%. The network has already succeeded in defining the epidemiology of rotavirus, while at the same time increasing its laboratory capacity, drawing greater attention to rotavirus in Asia, and identifying sites for future vaccine evaluation.

Regional Rotavirus Surveillance in Africa

Rotavirus surveillance in Africa and Asia gained its initial impetus from the agreements reached at a workshop organized by WHO in 1997, where discussion focused on the need to understand the epidemiology of rotavirus in Africa and Asia. In 1998 four workshops were held to train personnel from 18 African countries. The surveillance system, also initiated in 1998, was designed to cover samples submitted to laboratories and samples taken from hospitalized patients. As of 2003 the WHO Generic Protocol had been followed in processing some 30,000 diarrheal samples, from which approximately 7,000 strains of rotavirus were isolated. For screening the samples, the recommended technique is the ELISA test, and for genotyping, RT-PCR detection. The results showed that in Africa rotavirus is responsible for 20% to 40% of all diarrheal disease in children; it was more common in hospitalized children than those who have not been admitted; the infection affects 17% of children under 6 months of age, 75% of those under 12 months, and 83% those under 18 months; and its seasonal distribution peaks in the cold and dry months. With regard to the frequency of isolated G strains, the findings were as follows: G1, approximately 50%; G3, approximately 30%; G2, intermittent occurrence every 3 or 4 years; G4 and G8, sporadic isolation; G9, emerging throughout the world. Mixed serotypes are very common. Genotype P[6] is the most frequent, accounting for 50% to 60%, while P[8] is found in 35% to 40% of the cases. VP4 is unusual. In the future it is planned to carry out studies on the disease burden in the hospital network; develop regional laboratories for the typing of strains; expand surveillance to include the collection of additional data for specific studies on such topics as estimated costs, invagination, and others; identify sites for clinical vaccine trials; and continue to maintain joint cooperation with WHO, CVP, and RVP (CDC).

ROTAVIRUS SURVEILLANCE IN LATIN AMERICA

Ten Years of Hospitalizations for Diarrhea in Peru

As a part of a study of epidemiological surveillance for rotavirus gastroenteritis in hospitalized children, fecal samples of children admitted to the hospital for watery acute diarrhea and dehydration were collected between January 1992 and December 2002 (except during 1993). The samples were obtained from the first diarrheal stool passed by the child after admission to the hospital. Rectal swabbing was not used in any of the cases. The fecal samples were stored immediately at -20°C until they could be processed.

The children were eligible for inclusion in this sampling study if they were 2 to 24 months old; had a history of watery diarrhea without visible blood (based on information provided by the mother or the admitting physician); had had the first watery stool, as noted by the mother, within the last 72 hours, and presented clinical signs of dehydration classifiable as “some degree of dehydration” or “serious dehydration” according to the WHO standard. The presence of rotavirus particles in the fecal samples was examined by the ELISA technique using a commercial kit (Rotaclone[®], Meridian/USA). The results of this examination were reported as simply positive or negative, following the instructions of the manufacturer.

A total of 1,391 fecal samples were examined, and 574 (41%) proved to be positive for rotavirus. During 1992-1996 an average of 151 samples were taken annually, but 1997 saw a major distortion in the number of diarrhea cases treated in hospitals as a result of the warming trend associated with El Niño. The mean temperature that year was considerably higher than in previous years, virtually eliminating the winter season that normally occurs between May and August. This distortion extended into the first semester of 1998. During 1999-2002 the sampling rate was reduced to an average of 88 a year, due at least in part to the implementation of health care levels under the comprehensive health insurance program. The results of the study showed that during the 10 years of observing hospitalized children, rotavirus accounted for no less than 40% of hospital admissions for watery diarrhea and dehydration, and in each year of the study the seasonal nature of rotavirus gastroenteritis in hospitalized children was consistent, with the highest rate of cases during the coldest months of the year (May to August).

Economic Impact of a Vaccine: A Study in Peru

The objective of the study was to evaluate the disease burden of rotavirus diarrhea in Peru, the need for a vaccine, and the savings that it could provide in this country. To evaluate the disease burden of rotavirus diarrhea in Peru, published and unpublished studies on rotavirus as a cause of diarrhea in children were reviewed. The rotavirus detection rates in these studies were combined with the diarrhea incidence rates from several national surveys in estimating both the disease burden of rotavirus diarrhea and its medical costs.

Rotaviruses are an important cause of morbidity and mortality in Peruvian children. It is estimated that in the first five years of life 1 of every 1.6 children suffers an episode of rotavirus

diarrhea, 1 of every 9.4 receives medical care, 1 of every 19.7 needs to be hospitalized, and 1 of every 375 dies from this cause.

This represents approximately 384,000 cases, 64,000 consultations, 30,000 hospitalizations, and 1600 deaths a year. The cost per year of medical care alone for these children is approximately US\$ 2.6 million, not taking into account the indirect or social costs of the disease and the deaths that it causes.

Vaccination against rotavirus makes it possible to hold out the hope of reducing morbidity and mortality from diarrhea in Peru, but the vaccination regimen should be relatively inexpensive. In the future, cost-effectiveness analyses should include all the costs of rotavirus diarrhea, both medical and indirect or social, and the approved vaccines should be tested for both their ability to prevent deaths and their effectiveness with fewer than three doses. These three factors could increase the savings achieved with a rotavirus vaccine.

Estimates of Disease Burden in Argentina, Chile, and Venezuela

During 1997-1999 a collaborative prospective study was conducted to determine the disease burden imposed by rotavirus as a cause of medical visits and hospitalizations for non-bloody diarrhea in three large pediatric sentinel hospitals in Chile, Argentina, and Venezuela in children under 36 months of age.

In Chile and Venezuela the information on medical visits was based on emergency consultations, while in Argentina it was based on visits to the hospital outpatient clinic.

A total of 7,057 stool samples of non-bloody diarrheal disease in children under 36 months of age were collected and examined for rotavirus using the ELISA technique.

The medical visits and hospitalizations for rotavirus diarrheal disease represented 4%/4%, 5%/6%, and 9%/13% of all medical visits and hospitalizations in Argentina, Chile, and Venezuela, respectively, with statistically significant differences between the sites.

The rotavirus detection rates in the 5,801/1,256 fecal samples examined in medical visits/hospitalizations were 39%/72% in Argentina, 34%/47% in Chile, and 29%/38% in Venezuela. The seasonal pattern prevailed in the medical consultations at the three sentinel sites, with the highest rates during the cold months. The rotavirus associated with hospitalization has a marked peak in Venezuela between November and May, reflected in short hospital stays, but not in Argentina or Chile.

Extrapolation of the data from this study gave national estimates of 106,000/20,590 medical visits/hospitalizations for rotavirus diarrhea in Argentina, 53,042/8,036 in Chile, and 97,000/31,000 in Venezuela.

Argentina

In addition to the study of disease burden in Argentina reported above, a study of rotavirus epidemiological surveillance was undertaken based on prior studies and using a standardized working protocol and a network of seven sentinel units. The study was conducted between October 1996 and September 1998 in children under 3 years of age. The samples were collected during the first 24 hours, and the laboratories had a quality control system in place.

The study revealed the presence of rotavirus in 42% of 1,312 children with diarrhea and a seasonal pattern was confirmed, with the disease reaching its peak between April and June. The study also showed that 60% of the cases were in children under 1 year of age and 90% in children under 2. In the 490 samples analyzed, rotavirus G1P(8) and G2P(4) were predominant during the first year of life, and the most common types during the second year were rotavirus G1P(8) and G4P(8). Mixed infections accounted for 8% of the samples, and 2% of samples were not typed for the G serogroup. On the other hand, during 1999 rotavirus G9P(8) was found in 16 of the 88 rotavirus strains analyzed, with a rate as high as 41% in the southern part of the country.

Diversity of Rotavirus Serogroups in Brazil

A broad diversity of rotavirus serogroups are observed in Latin America. Virological surveillance for rotavirus basically reveals the G and P genotypes using PCR (multiplex) laboratory methods, which are now considered the gold standard and recommended in the WHO Generic Protocol.

Research groups are conducting studies in the five geographical regions of Brazil with support from the Ministry of Health and various national and international organizations: the Evandro Chagas Institute SVS/Ministry of Health, the Federal University of Goiânia, the Federal University of Bahia, the Federal University of Rio de Janeiro, the Oswaldo Cruz Foundation/Ministry of Health, São Paulo State University, and Londrina State University.

Rotavirus infection in Brazil presents a seasonal pattern, occurring with greater incidence during the months between April and September. In keeping with observations in many parts of the world, several genotypes of the virus circulate in this country. Although genotype G5 was very important up until the end of the 1990s, recent studies have shown that genotype G9, which was not identified previously, is now very frequent.

A recent study (1998-2003) in the northern region of the country, in the metropolitan area of Belém (a tropical area), showed that genotypes G1 (12%) and G2 (20%) were the most frequent, followed by genotype G9 (10%). A large proportion of the G strains that were identified (50%) could not be classified using the PCR or monoclonal antibody techniques. Among the P genotypes, the most frequent were P4 and P8, followed by P6. Again, a large proportion of the P strains studied could not be classified. G9 should be regarded as an emerging genotype in this region.

In the cities of Goiânia and Brasília (in the midwestern region of the country), genotypes G1, G9, P8, and P6 were the most frequent during 1998-2002. Mixed infections and samples that could not be typed were also frequent.

In Salvador (in the northeastern region), during 2001-2003 a low prevalence of rotavirus infections (7%) was observed in precarious urban communities. If the 40 samples analyzed, the most frequent genotypes were G1, G9, P8, and P6. Some mixed infections and unclassifiable samples were also observed.

In the cities of Rio de Janeiro and Niterói (in the southeastern region of the country), during 1996-1997 the genotypes G1 and G5 were more frequent than genotypes G8 and G10, and mixed infections were also observed. Two years later, during 1997-1999, new studies showed that genotypes G1P8, G2P4, G3P8, and G4P8 accounted for almost 70% of the genotypes. In addition, the appearance of genotype G9 (15%) has also been confirmed.

Other recent studies in Rio de Janeiro (2000-2001) have shown that in hospitalized children the most common genotypes were G1, G2, G3, and G4 (representing 50%). Less common genotypes, including G5 and G9, mixed infections, and unclassifiable strains accounted for the remaining 50%. Also, it was shown that different genotypes were circulating at the same time in one health unit and that genotype G9 was the second most frequent agent.

The same pattern was observed in the state of Espírito Santo (in the southeastern region). During an outbreak of rotavirus infection, the analysis of 55 positive samples revealed that genotype G1P8 was the most frequent and that G9P8 was also present. Thus it has been concluded that in the states of Rio de Janeiro and Espírito Santo different genotypes have been circulating at the same time and that G9 is the second most common genotype.

In the city of São Paulo (April 2000-May 2001) the main genotypes observed were G1 (39%), G2 (17%), G9 (14%), and G4 (9%). At the same time, however, the uncommon genotype P10 was observed in 25% of the strains characterized.

Finally, data from an outbreak of rotavirus infection during June and July 2003 in the city of Caxias do Sul, Rio Grande do Sul (in the southern region of the country, which is a temperate area) indicate that the responsible genotype was G9, either alone or in association with G1.

Thus it may be concluded that genotype G9 is an emerging strain in Brazil. The most common genotypes in the country represent between 50% and 80% of the circulating genotypes. The circulation of G5 is diminishing dramatically. P6 and P10 are also considered to be emerging.

Rotavirus continues to be a great challenge because it infects a broad diversity of human and animal species, thus permitting recombination and the appearance of new emerging genotypes. For this reason, the implementation and quality surveillance is fundamental for monitoring the emergence of new genotypes.

Risk Factors for Children <5 Years Being Hospitalized for Diarrhea in Colombia

During 2000-2001 the Colombian National Institute of Health conducted a study to explore the possible correlation between rotavirus infection and severity of diarrhea, as well as to identify the environmental and socioeconomic factors, including lack of access to health services, that may have favored the development of dehydration from diarrhea in children under 5 years of age.

A case-control study was designed in which 290 children under 5 were selected according to clinical criteria recommended by WHO. The case-control ratio was 1:1. All the subjects were tested using the ELISA technique for rotavirus. In addition, both descriptive and logistic analyses were performed, with selected variables for the value of p and a log-likelihood ratios of < 0.05 .

The following risk factors were identified, among others: ignorance of the mother about diarrhea (OR=4.05; CI: 2.21–7.46), lack of awareness about the signs of dehydration (OR=18.26; CI: 8.78–38.72), and low birthweight (OR=6.07; CI: 3.07–12.13). Other risk factors had to do with knowledge, attitudes, and practices, particularly those related to hand-washing before and after using the toilet and before feeding a child, as well as access to and quality of promotion and prevention programs implemented by the Government. There was also a significant risk of rotavirus being associated with dehydration (OR= 3.46; CI: 1.71–7.00).

The results show that the complications of diarrhea can be diminished considerably with primary care strategies. It was troubling that the mothers lacked basic prevention skills, particularly because the population in question belonged to the health insurance system and had easy access to health services. These findings suggest the importance of systematically evaluating public health programs to ensure that their goals are being met.

The study also found a correlation between rotavirus infection and dehydration from diarrhea. It is considered essential to implement a surveillance system that is linked to other countries of the Region in order to evaluate the cost-effectiveness of introducing a specific vaccine against this viral agent once it is available on the market.

Incidence of Rotavirus Disease and Intestinal Invagination: Preliminary Data from a Prospective Study

The objective of this one-year study was to estimate the disease burden of rotavirus infection in children under 3 years of age and to estimate the incidence of intestinal intussusception in boys and girls under the age of 2 in selected countries of Latin America. It was a hospital-based multicenter prospective study. The Brighton Working Group definition of case of intussusception was used.

The study examined 7,520 girls and boys who were suffering from a diarrheal episode, 73% of whom were hospitalized.

The preliminary results showed that in a total of 5,856 samples examined, 49% (2,878) were positive for rotavirus.

According to these same preliminary results, the incidence of invagination in the countries participating in the study were as follows:

Country	Incidence per 100,000 population per year
Panama	56
Argentina	54
Mexico	54
Costa Rica	39
Dominican Republic	15

Note: The incidence was calculated using the Brighton definition, which includes confirmed, probable, possible, and suspected cases.

Retrospective studies conducted in three other countries of Latin America found the following annual prevalences: in Chile, among children under 2 years old, 32 per 100,000 population; in Venezuela, among children under 1 year, 35 per 100,000 population; and in Panama, in children under 1 year, figures ranging from 16 to 54 cases per 100,000 population.

Rotavirus Studies in Mexico

Following are the results from studies carried out in second- and third-level care units under the jurisdiction of the Mexican Social Security Institute (MSSI).

Between 1990 and 2001 Mexico saw a notable reduction in the frequency of diarrhea in children under 5, with a drop in the monthly average from about 1,200 to 300 cases. During the period from 1990 and 1994, every month a total of around 2000 children under 5 were hospitalized for diarrhea in all the MSSI units, and nearly 1,000 them were are children under 1 year old.

A study conducted in Mexico City hospitals showed that 40% of all diarrheal cases were caused by rotavirus.

With regard to the effectiveness of the vaccine, it was found that the prevention rates with one dose of vaccine were 38% for infections, 77% for cases of diarrheal disease, and 87% for serious cases diarrheal disease; with two doses, the rates increased to 60%, 83%, and 100%; and with three doses, the protective efficacy was 66%, 92% and 100%.

Another study examined the economic cost of the cases treated by the MSSI. The average cost per episode was US\$ 670.00. Of this amount, the MSSI pays 86% (US\$ 615.00) while the family pays

Rotavirus and Intestinal Invagination in Venezuela

The first licensed vaccine against rotavirus was eliminated from the vaccination series since it was found to be associated with cases of intestinal invagination. As a result, studies involving new vaccines must now investigate the epidemiological and clinical manifestations of this condition.

Accordingly, a retrospective and prospective study of these cases was undertaken in the Venezuelan state of Carabobo. In the retrospective study, clinical and epidemiological data were reviewed in patients with intestinal invagination admitted to eight of the state's hospitals between January 1998 and December 2001. The prospective study began in 2002. The results showed that the pattern of clinical and epidemiological manifestations associated with intestinal invagination in the state of Carabobo were similar to those described by other studies: the condition is more frequent in males than in females ($p < 0.05$) and in the lower and marginal socioeconomic strata ($p < 0.05$). The seasonal distribution of invagination cases, however, is not characteristic. The annual rate during 1998-2003 was 38 per 100,000 children. The study presents information on the incidence of intestinal invagination and its epidemiology, including very useful data for a country in which a new rotavirus vaccine is being tried.

Update on Rotavirus Activities in Latin America

GlaxoSmithKline has completed phase II studies of its monovalent live attenuated oral vaccine against human rotavirus (type G1, P8). In these studies, carried out in five countries of Latin America, three countries of North America and Europe, and three countries of Asia and Africa, more than 7,200 children received this human rotavirus vaccine (HRVit), which was administered at 6-12 weeks of age with a second dose approximately two months later.

The results of these preliminary surveys indicate that the HRVit vaccine is well tolerated and sufficiently safe to go on to the large-scale phase III studies.

The preliminary results of vaccine efficacy studies carried out in Latin America show that two doses prevent nearly 85% of severe diarrheal disease caused by rotavirus (92% of severe diarrheal disease caused by rotavirus G1 and 80% of severe diarrheal disease caused by rotaviruses other than G1).

The information gained in the studies so far provides a solid basis for embarking on large-scale phase III studies.

Clinical trials of a rotavirus vaccine

Currently, two vaccines against rotavirus are in the clinical trial phase: Rotarix™ (GSK) and Rotateq™ (Merck). Both have already been subjected to phase I and II clinical trials and are ready for phase III studies in several countries.

Rotarix™ (GSK), RIX 4414, is a monovalent live attenuated oral vaccine (genotype G1, P1A[P8]). This vaccine shares neutralizing epitopes with genotypes G3, G4, and G9. It is administered in two doses beginning at 6-12 weeks of age.

A phase IIb study was carried out in Brazil (n=900), Venezuela (n=920), and Mexico (n=900), to assess the vaccine's efficacy, immunogenicity, reactogenicity, and safety, as well as to study the dosage. There were 569 subjects in this double-blind, placebo-controlled prospective study. In terms of reactogenicity, the vaccine was not associated with an increase in adverse reactions when the first and second dose were compared with placebo, when the concentration was increased, or when it was administered concomitantly with other vaccines. With regard to safety, no difference in serious adverse events was observed in comparison with the placebo group after the vaccine was administered, nor was there an increase in rates of intestinal invagination compared with basal rates. However, the sample was not sufficiently large to draw conclusions about the occurrence of intestinal invagination.

The clinical trials demonstrated that the vaccine and is well tolerated and safe, and that it has an immunizing effect in both developing and developed countries. Moreover, it is highly effective and confers cross-protection. The phase III study is currently starting up in 12 countries of Latin America, covering a population of 60,000 children, and it should be concluded in September 2004.

Rotaviral Gastroenteritis Outbreak in Jamaica

A gastroenteritis outbreak affecting all age groups was first reported in epidemiological week 22 of the current year. By week 36 the number of cases had declined and the outbreak was on the wane. A total of 4,054 cases were reported between weeks 23 to 31, with 93% (3,771) of them concentrated on the parishes of Kingston and Saint Andrews. During this same period, 12 deaths were investigated, 8 of which were associated with gastroenteritis.

The cases of gastroenteritis in children under 5 were determined to be associated with rotavirus, since of 25 of 54 samples (46%) analyzed using the ELISA technique showed evidence of rotavirus. The initial genotypical characterization showed that the common strains of rotavirus were the most prevalent ones.

A study of the Merck vaccine has been under way in the parish of Kingston since March 2002. However, no connection has been found between the vaccine strain and the outbreak of rotaviral gastroenteritis. Investigation of the outbreak, including the characterization of strains and the plotting of their occurrence, is still under way.

The existence of an efficient gastroenteritis surveillance system has made it possible to find cases outside the expected seasonal pattern in this country.

SURVEILLANCE PROJECTS IN LATIN AMERICA

Brazil

In Brazil there is a surveillance system for cases of diarrheal disease in which information can be collected on the basis of aggregate data. For the diagnosis of rotavirus, the clinical samples are sent to state laboratories that carry out serology tests and are in a position to refer them to two national laboratories (FIOCRUZ and the Evandro Chagas Institute) for PCR.

Since 1994 a national information system has been being developed for the collection, consolidation, and transmittal of surveillance data on diarrheal disease. The system has already been implemented in 3,854 municipios (70% of the municipios in the country).

For data on hospitalizations, a national computerized information system has been in place since 1984 which collects data on all hospitalizations that were paid for with public funds, including hospitalizations in the private network. For data on mortality, a national computerized system has been collecting data on all death certificates issued in the country since 1979.

In 2002 the information system recorded 880,388 cases of diarrheal disease in children under 5 in the country as a whole.

With regard to mortality, even though the rate has declined steadily in the longitudinal studies, 3,596 deaths from diarrheal disease in children under 5 were recorded in the year 2000 (the last one for which definitive information is available). This figure represents a coefficient of 22 deaths per 100,000 children under the age of 5. In the last two years an annual average of 282,500 hospitalizations for diarrheal disease were reported in children under 5, for a rate of 17.12 per 1,000 children in that age range. In terms of costs, the average annual expenditure for the hospitalization of children under 5 with diarrhea has been US\$ 18,923,118.00, with an average of US\$ 66.22 per hospitalization.

With regard to the proportion of rotavirus diarrhea relative to all cases of diarrhea in children under 5, a recent report from the state of Minas Gerais cited a figure of 32.6% for hospitalized patients and 3.4% for outpatients. The outpatient proportion is higher in three other studies conducted in other regions, with reports ranging from 8.5% to 29.6%. In 2003 the Rotavirus Surveillance Project was implemented in localized sentinel sites at hospital units in the five regions of the country.

The selection of units and municipios followed the WHO recommendations for surveillance studies and the investigation of rotavirus disease burden. Training in the state reference laboratories has been under way since 2001, and the training of health unit personnel to identify cases and collect samples is scheduled for December 2003.

El Salvador

The study of rotavirus in El Salvador has been aimed at understanding the following aspects of its epidemiology:

- G serotypes and P genotypes of the circulating rotavirus;
- Seasonal pattern of rotavirus infection;
- Frequency of concurrent infections involving more than one serotype or genotype;
- Possible substitution of one serotype or genotype for another during the course of the year;
- Epidemiology of rotavirus infection in children under 5;
- Economic impact of rotavirus disease in assessing the cost-benefit of applying a future rotavirus vaccine;
- Disease burden of rotavirus;
- Incidence of intestinal intussusception in children <5 years old;
- Incidence of intestinal intussusception associated with rotavirus infection;
- Possible seasonal aspects of intestinal intussusception.

The study will be carried out in the following two hospitals:

- Dr. Juan José Fernández National Hospital of Zacamil (Zacamil Hospital)
- Benjamín Bloom National Hospital for Children (Bloom Hospital)

The characteristics of the two study hospitals are as follows:

Hospital Bloom: 3rd level of care, 280 beds, population covered: 171,145 children <5 years old. Estimated admissions for diarrhea as of 2001: 639 children <5 years a year.

Hospital Zacamil: 2nd level of care, 255 beds (55 pediatric), population covered: 69,185 children <5 years old. Admissions for diarrhea as of 2001: 900 children <5 years a year.

Paraguay

Diarrhea is recognized as a serious public health problem in Paraguay, where it is one of the leading causes of morbidity and mortality in children. Health care in Paraguay is the responsibility of two subsectors: the public and the private. The public subsector consists of the Ministry of Public Health and Social Welfare, the Institute of Social Welfare, the military and police health services, and the National University of Asunción, with its Clinical Hospital Center.

Paraguay does not have a surveillance system for characterizing the patterns of rotavirus diarrheal disease and the diversity of the circulating viruses. It is therefore necessary to establish a sentinel surveillance system that will generate information to be used in making public policies for prevention once a vaccine becomes available.

Purpose of the proposal

To establish a sentinel surveillance system for monitoring the impact of a vaccine, once it is introduced, through attainment of the following objectives:

- Incorporate a rapid laboratory diagnostic method for confirming rotavirus cases;
- Estimate the incidence of hospitalizations associated with rotavirus in the monitored population;
- Characterize the patterns of rotavirus diarrheal disease in the population under surveillance by age group and seasonal occurrence;
- Estimate the proportion of all hospitalizations for diarrhea attributable to rotavirus;
- Identify the prevalence of the different types of rotavirus in the population under surveillance.

The study will be conducted in children with diarrhea under the age of 5 who are brought in for hospital treatment at one of the four selected sentinel institutions.

The disease burden will be estimated for each sentinel center. Participation in this study does not involve any physical risk for the patient; the proposal was submitted to the Bioethics Committee at the National University of Asunción.

It is planned to execute the project over a period of two consecutive years.

Venezuela

In Venezuela, the Ministry of Health and Social Development and the National Institute of Public Health have prepared a project for the epidemiological surveillance of rotavirus in three States of the country, selected on the basis of morbidity profile and operational feasibility: the Capital District, Carabobo, and Falcón. The purpose of the study is to develop laboratory surveillance of rotavirus to determine its prevalence and seasonal distribution as well as the age of the affected groups. The population to be investigated will consist of children under 5 with diarrhea who are brought in to hospitals in the states included in the study. They must meet the established criterion, namely: an episode of diarrhea with three or more semiliquid stools within 24 hours, or a stool containing mucus and blood.

In each state, 25 cases of diarrhea a month (300 cases a year) will be included in the surveillance study over a period of two years. The samples will be selected at random until 6 cases are identified each week.

Demographic, clinical, and laboratory data will be collected and noted in the epidemiological record designed for this purpose, to be filled out by the attending physician and completed by the

laboratory staff. The diagnosis of rotavirus will be made using the ELISA technique once the personnel at the National Institute of Hygiene in Caracas have been trained.

Periodically, 10% of the samples will be sent to the Institute of Biomedicina–Fuvesin for quality control. The samples that are positive for rotavirus will be sent to the reference laboratory selected by PAHO to determine the G and P serotype.

CAREC Member Countries

It is proposed to conduct a study in four countries of the English-speaking Caribbean community (Guyana, Saint Vincent and the Grenadines, Suriname, and Trinidad and Tobago) to strengthen the surveillance of rotaviral gastroenteritis. Following the PAHO/WHO Generic Protocol, the proposed study is to be based on active surveillance and research of rotavirus in fecal samples from children under the age of 5 who are treated for diarrhea at sentinel hospitals.

These hospitals are:

- Georgetown General Hospital, Guyana
- University Hospital, Suriname
- Kingstown General Hospital, Saint Vincent and the Grenadines
- Eric Williams Medical Sciences Complex, Hospital for Sick Children, Trinidad and Tobago

The demographic characteristics of the population and the epidemiological patterns of rotaviral gastroenteritis will be determined jointly, and the rotavirus groups and serotypes prevalent in these countries will be identified.

The data collected will be analyzed to determine incidence rates, seasonal trends, and prevalent serotypes, to serve as a basis for designing future surveillance programs in the CAREC member countries.

FUTURE COUNTRY PARTICIPATION

Ecuador

In this country, the only study on the incidence of rotavirus was conducted over a period of 28 months during 1978-1980 in patients admitted to a Guayaquil Welfare Board hospital by a team of researchers from the University of Akita in Japan and the Ecuador's Leopoldo Izquieta Pérez National Institute of Hygiene. Electron microscopy was used to identify rotavirus, and its occurrence was found to have a seasonal pattern, following climate changes measured by temperature and relative moisture. The highest frequency of cases and percentage of confirmed rotavirus diarrheal disease occurred during the summertime, which is characterized by lower temperatures and a dry or less rainy season. The study was published in the *Revista Ecuatoriana de Higiene y Medicina Tropical*, vol. 34, January-June 1984.

Morbidity and mortality from diarrhea has declined in recent five-year periods, but it continues to be a major cause of illness and death, with a highly heterogeneous distribution in the 22 provinces and varying degrees underreporting of cases and deaths due to acute diarrhea. Data from 1997 show that the highest recorded case rates were in the Amazon region, both in children under 1 year (209.9 per 100,000) and in preschool children (37.8 per 100,000). The coastal area had the second highest rate for infants (136.1 per 100,000) and the third highest for children (19.1 per 100,000), while the highlands had the lowest rate in infants (94.6 per 100,000) and the second-lowest in preschool children (24.7 per 100,000).

Proposal

It is proposed to implement epidemiological surveillance of cases of acute watery diarrheal disease with dehydration admitted to the public pediatric hospitals in Quito and Guayaquil with the participation of scientific associations. The ELISA technique will be used to identify cases of rotavirus at area laboratories in Quito and the National Health Institute Laboratory in Guayaquil. The samples will be preserved and sent to the reference laboratory in Guayaquil for PCR processing to identify the serotype. In addition, the baseline of intussusception frequency will be estimated through a retrospective study in the same hospitals.

Requirements

It will be necessary to train personnel in Quito and Guayaquil and obtain a supply of reagents. A workshop will be convened to discuss the protocol with staff from the national and provincial EPIs, participating pediatric hospitals, the national health laboratory, and PAHO/WHO.

Argentina

This country is completing its work on developing an epidemiological diarrhea surveillance system based on a network of sentinel units within the framework of a comprehensive surveillance program carried out by the National Epidemiological Surveillance System (SINAVE), the Ministry of Health's Surveillance Program (VIGIA), and the National

Administration of Health Laboratories and Institutes (ANLIS). It is committed to taking into account the WHO Generic Protocol, and it also intends to conduct a survey of health services following the recommendations contained therein. The support of PAHO and other international agencies will be important in fulfilling some of these objectives.

Type of sampling. The two hospitals will use nonprobabilistic sampling of consecutive cases as they are incorporated into the study – i.e., five children under <5 admitted for diarrhea in each epidemiological week.

Chile

In 1992 the annual frequency of diarrheal episodes was estimated at 1.5 in children under 5 years old. The frequency has declined to the point that diarrhea is no longer among the four leading causes of morbidity in children in this age group. Mortality has fallen sharply, from 3.8 per 100,000 children in 1990 to 0.5 in 2001. Diarrhea is on the list of notifiable diseases, and a sentinel center strategy has been adopted for the surveillance of diarrhea cases and their etiology. The surveillance of cases yields incidence data by age and sex from 32 sentinel centers, corresponding to a population of 100,473 children under the age of 5 (7% of all children that age in the country), which is reported daily using a special computer system. In the year 2003, 6,340 cases of diarrhea were reported in children under 5, for a rate of 61 per 1,000 children in that age group, which rises to 89 per 1,000 children in the group under 1 year old. In terms of etiology, the study has identified rotavirus as one of the principal agents seen in hospitalized patients. A collaborative study with Argentina and Venezuela showed that 34% of the cases treated at outpatient services were due to rotavirus. Data from hospital discharge records, categorized according to ICD-10, show that “rotaviral enteritis” ranks in second place.

Investigators at the University of Chile and other research groups have carried out or are carrying out studies that have documented the seasonal variation in the incidence of rotavirus, and they have identified the prevalent serotypes and their variations over time.

The Ministry of Public Health Department of Epidemiology, the Institute of Public Health National Reference Laboratory, and the University of Chile have maintained contacts in addressing the subject and could coordinate sentinel surveillance.

In addition to the foregoing, the country is participating in phase III clinical trials to test the candidate vaccines against rotavirus.

Proposal

It is proposed to strengthen epidemiological surveillance of cases of acute watery diarrheal disease with dehydration treated at the sentinel centers with support from network of Institute of Public Health (ISP) and University of Chile laboratories as well as the national reference laboratory. Surveillance will make it possible to identify the magnitude and variations of aqueous gastroenteritis due to rotavirus and determine the distribution of serotypes, thus paving the way for evaluation of the impact of the vaccine when it is introduced in the future. It is also proposed

to strengthen laboratory capacity and homogenize laboratory techniques for ELISA diagnosis in hospitals belonging to the public service network.

Requirements

Advisory services and financial support are needed to guarantee the availability of reagents for laboratory diagnosis in hospitals, the identification of rotavirus serotypes in the ISP and University of Chile laboratories, and the recruitment of human resources for the national reference laboratory to type the rotavirus strains.

Uruguay

Diarrheal disease (DD) continues to account for significant morbidity and mortality, basically in children under the age of 5. Even though the figures have declined since oral rehydration guidelines have been promoted and applied to hospitalized cases, children with serious DD continue to be hospitalized. Each year they represent about 6% of admissions at the Pediatric Hospital of the Pereira Rossell Hospital Center, the country's only pediatric referral hospital for children treated in the public sector.

In Uruguay, acute diarrheal disease (ADD) currently ranks tenth as the cause of death in children under 1 year old.

Of the etiologic agents investigated, rotavirus is one of the leading causes.

Starting in 1982, when rotavirus in children with diarrhea began to be investigated, the studies have reported varying frequency of the disease, depending on a number of factors: time of year, number of patients included, socioeconomic level, outpatient or hospitalized cases of diarrhea, diagnostic technique utilized, etc. Thus the studies show prevalences ranging from 13%-19% up to as high as 70%. To determine the true impact of rotavirus infection and identify the serotypes and genotypes, it will be necessary to conduct systematic ongoing studies that include different variables.

In light of the foregoing situation, our plans call for incorporating surveillance of viral diarrheal disease into a centralized system in order to better understand the overall reality of the disease in Uruguay and adequately integrate surveillance into the regional network.

This means incorporating new diagnostic techniques (RT-PCR) in order to be consistent with the rest of the Region and participate jointly with the other PAHO members in the development of human and technical resources, training, discussion meetings, etc., and in access to economic resources for strengthening the regional surveillance network.

Although PAHO recommends integrating rotavirus laboratory surveillance into the established regional laboratory network for the surveillance of poliomyelitis, Uruguay does not have a laboratory for polio surveillance and the country therefore proposes to develop a national rotavirus reference laboratory supported by national epidemiological data.

Bolivia

In 2004 and 2005 it is planned to conduct studies to determine the rotavirus disease burden and its epidemiology in hospitalized children under the age of 5 in the city hospitals of La Paz. It is also planned to conduct a pilot study at hospitals in Cochabamba, Santa Cruz, and Beni so that a rotavirus surveillance network will be in place in the near future.

Colombia

The following actions have been taken:

1. Determination of the rotavirus disease burden. A study has been scheduled to start in October 2003 to determine the rotavirus disease burden following the WHO Generic Protocol, December 2002 version. The study will be conducted in three cities of the country (Bogotá, Cali, and Cartagena), located in three of the most densely populated regions in Colombia. As it has been seen in the analysis presented in this document, each of these regions has differences in the trend of mortality from diarrhea over the last three years, as well as in socioeconomic, geographic, and specific cultural characteristics.

2. Public Health Laboratory sentinel surveillance system. The sentinel surveillance currently being carried out in eight municipios of Colombia will be strengthened by the addition of the three capital cities where the study of rotavirus disease burden is based. This surveillance system will determine the seasonal nature and proportion of agents of ADD – i.e, parasites, bacteria, and rotavirus.

3. Strengthening of the diarrhea surveillance system. The sentinel surveillance systems will be strengthened to detect the principal etiologic agents of ADD, to determine the morbidity and hospitalization rates for diarrhea, and also to coordinate with the National Public Health Surveillance System (SIVIGILA). Finally, local political priority for rotavirus will be promoted.

CONCLUSIONS

- Some of the outstanding findings were that approximately 50% of hospitalizations for diarrhea are due to rotavirus; that these episodes usually occur before the age of 12 months, and that they are often accompanied by moderate to serious dehydration, thus identifying the disease as a public health problem.
- The various epidemiological surveillance studies that have already been conducted and made available in some of the Latin American countries, even though they present partial data in most cases, provide hard data and similar findings regarding the incidence of rotavirus disease in many countries of the Region.
- Among the highest priorities of the pharmaceutical industry is the development of two new vaccines against rotavirus, which are about to reach phase III testing and will soon be registered and made available on the market. Both are very promising in terms of efficacy.
- Better economic data are needed for cost-benefit and cost-effectiveness studies, for which it will be necessary to know the cost of the vaccine (which has not yet been determined).
- The identification of rotavirus genotypes and serotypes will help us to better understand the vaccine that we need.

RECOMMENDATIONS

General

- The rotavirus epidemiological studies that have already been approved in the Region should be initiated as soon as possible, and those that have already been initiated and those awaiting approval should be accelerated.
- A database should be created similar to those that already exist for the surveillance of polio, measles, and rubella so that the results of the various studies that will be being conducted in the countries of the Region can be compared.
- The methodology for conducting economic studies should be standardized so that they will be comparable and so that cost-benefit and cost-effectiveness studies can be carried out.
- Once the countries have obtained epidemiological information on the disease, disease burden studies should be carried out to serve as a basis for taking the necessary preventive steps, including the probable introduction of a vaccine.

Laboratory

- The rotavirus laboratory network should be integrated into the network already established in the Region for the surveillance of polio.
- In every case of ADD a stool sample approximately 5mL should be collected, preferably on the day the patient is admitted to the hospital, and then placed in a sterile screw-top plastic container and properly labeled.
- All the fecal samples should be transported to the laboratory at 4-8°C and kept at this temperature if they are going to be processed within 7 days after they were collected; if the laboratory tests are going to be conducted within two months, it is recommended to store them at -20°C; and if they are going to be processed after two months, they should be kept at -70°C. It is important to remember that freezing/thawing cycles are undesirable, since they diminish the viability of the virus.
- To ensure that the results from the different countries in the Region will be comparable, all the fecal samples collected for purposes of rotavirus laboratory surveillance should be examined to detect the presence of rotavirus antigen using one of the commercial ELISA kits recommended in the Generic Protocol.
- The RT-PCR technique should be used for genotyping the viruses.



**Regional Meeting on Implementation of
Epidemiologic Surveillance for Rotavirus
Lima, Peru; 4-5 September, 2003**

Thursday 4th September 2003		
8:00	Registration	
Opening of the meeting		
8:30	Dr. Luis Eliseo Velásquez, PAHO Representative Perú (a.i) Dr. Jon Andrus, Chief IM/PAHO, Washington, DC Dr. Duncan Steele, WHO/Geneva Dr. Alvaro Vidal Minister of Health, Perú	
9:00	CVP: Dr. Julie Jacobson RVP: Dr. Joe Bresee Sabin: Dr. Ciro de Quadros	
9:15	Introduction and Objectives of the Meeting	Carlos Castillo-Solórzano PAHO
Session I: General Topics of Rotavirus Surveillance		
9:30	Rotavirus Epidemiology and Disease Burden: Global and Regional Estimates	Duncan Steele WHO
9:45	Rotavirus Epidemiology in The Americas	Salvador García PAHO
10:00	Overview of economic costs of Rotavirus	Richard Rheingans Emory University
10:30	Laboratory Surveillance Summary	Jon Gentsch CDC
10:45	Discussion	
11:00	Break	
11:15	Update on Rotavirus Vaccine Development	SueAnn Costa Clemens
11:30	Update on Rotavirus Vaccine Development	Chris Mast
11:45	Discussion	
Session II: Rotavirus Surveillance		
12:00	Regional RV Surveillance Experiences: Asia	Joe Bresee CDC/ADIP
12:15	Regional RV Surveillance Experiences: Africa	Duncan Steele WHO
12:30	Lunch	
	Rotavirus Surveillance in Latin America	
14:00	10 years of Hospitalization due to Diarrhea in Peru	Eduardo Salazar Lindo
14:15	Economic Impact of the Vaccine, a Study in Peru	Mary Penny
14:30	Estimation of disease burden in Argentina and Chile	Jorge Gomez
14:45	Diversity of Rotavirus Serogroups in Brazil	Jose Paulo Leite
15:00	Risk Factors for Hospitalization due to Diarrhea in Children < 5 years old in Colombia	Diana Carolina Cáceres
15:15	Incidence of Rotavirus disease and intussusception – preliminary data for a prospective study	Miguel O' Ryan
15:30	Break	
15:45	Cost of Rotavirus disease in Mexico	Raul Velazquez
16:00	Intussusception and Rotavirus in Venezuela	Rosabel Gonzalez
16:15	Update Rotavirus Activities in Latin America	Bruce Ines
16:30	Phase III Study of a Rotavirus Vaccine	Alexandre Linhares
16:45	Gastroenteritis Outbreak in Jamaica	Erica Reynolds
17:00	Discussion	
17:30	Closing Remarks	

Friday 5th September 2003		
Session III: Rotavirus Agendas		
8:30	Rotavirus Agenda: WHO RV Vaccine Program	Duncan Steele WHO
8:45	Rotavirus Agenda: CVP rotavirus activities	Julie Jacobson CVP
9:00	PAHO's Rotavirus Activities Agenda	Salvador García PAHO
Session IV: Discussion of Common Issues of Surveillance Projects in Latin America		
9:15	Generic Protocol for Rotavirus Surveillance and Disease Burden Estimates	Reina Turcios CDC/ADIP
9:30	Venezuela	Francisco Larrea
9:45	El Salvador	Carlos Flores
10:00	Paraguay	Norma Coluchi
10:15	CAREC	Rosa Salas
10:30	Brazil	Eduardo Hage Carmo
10:45 Break		
11:15	Discussion: Case Definition Ethical Issues Laboratory Methods Coordination	Salvador García / Reina Turcios
Session V: Additional Countries' Participation		
11:30	Diarrheal Illness in Children <5 years old, Rotavirus Investigations and Future Perspectives on Rotavirus Surveillance in Other Countries: Argentina, Chile, Uruguay, Bolivia, Peru, Ecuador, Colombia, Mexico:	Ministry of Health and Researchers
Session VI: Wrap-up		
12:00	Future directions: Resources for surveillance Other Outcomes Projects	WHO, PAHO, CVP, ADIP, Sabin Institute, Industry
Session VII: Closing Remarks		
12:45	Final Report: Conclusions and Recommendations	
13:00	Closing Remarks and Lunch	