

## Regional meeting for the Americas assesses progress against rotavirus<sup>1</sup>

Rotavirus (RV) disease is one of the most important causes of diarrhea-related morbidity and mortality in the world. RV mainly affects children under 5 years of age, causing diarrhea and sudden vomiting, together with fever in 30%–50% of the cases. 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 higher mortality.

For the world as a whole, each year there are an estimated 111 million cases of rotavirus-related diarrhea, 25 million outpatient consultations, 2 million hospitalizations, and 440 000 deaths, with 82% of the deaths taking place in developing countries. In the Region of the Americas, RV causes approximately 75 000 hospitalizations and 15 000 deaths each year.

While a number of studies have been conducted on rotavirus in the Americas, there is need for more high-quality data on the disease so that each country can take the most appropriate steps to prevent infections and to be in a position to decide on introducing a vaccine when one becomes available.

To provide an update on the fight against rotavirus in the Region of the Americas, a meeting was held in Lima, Peru, at the beginning of September 2003 (1). The meeting brought together representatives from a number of different countries and institutions, including the Pan American Health Organization (PAHO), ministries of health, the Centers for Disease Control and Prevention of the United States of America, the pharmaceutical industry, and vaccination programs. The meeting was intended to share knowledge about rotavirus epidemiology in the countries of the Region, discuss progress in the development of new vaccines, and describe experiences with surveillance.

**Key words:** rotavirus, diarrhea, vaccines, infant, Americas.

### SEEKING A SAFE, EFFECTIVE VACCINE

In 1998 it appeared that there was good news on rotavirus, with the introduction of a vaccine to protect against infection (2). Called RotaShield, the vaccine was produced by Wyeth Lederle Vaccines. Research funded by Wyeth had shown that three

<sup>1</sup> Based on: (1) Pan American Health Organization, Family and Community Health Area, Immunization Unit. Regional Meeting on the Implementation of Rotavirus Epidemiological Surveillance: generating information for decision-making. Washington, D.C.: PAHO; 2003.

oral doses of the vaccine prevented many cases of rotavirus infection among infants and reduced the severity of the infections that did occur. The Government of the United States of America had reviewed and approved the vaccine. Between October 1998 and July 1999 doctors in the United States administered more than one million doses of that Wyeth vaccine.

However, an unexpected problem with RotaShield led to the vaccine's being withdrawn from the market (2). Data from the United States' national system for monitoring vaccine performance indicated that in the two weeks after being vaccinated with RotaShield a very small number of infants might develop a potentially fatal intestinal blockage called intussusception. After the United States pulled the vaccine from the market, no other country would use it. In addition, that experience with RotaShield meant that other companies seeking to develop a rotavirus vaccine would need to conduct much larger safety trials to check for the possibility of rare adverse events such as intussusception.

Since RotaShield was withdrawn from the market in 1999 the search for effective vaccines has continued. Within the next few years there may be several vaccines available on the world market. Two of the pharmaceutical companies that are closest to bringing a new vaccine to market are GlaxoSmithKline (GSK) and Merck, according to a PAHO report on the rotavirus meeting in Lima (1) and other sources (2, 3). The GSK vaccine is named Rotarix, and the Merck one is RotaTeq. Both of those vaccines have undergone phase I and II clinical trials, and phase III studies are now in progress.

GSK's Rotarix is a monovalent live attenuated human RV oral vaccine that is administered in two doses, beginning at 6–12 weeks of age (1). Results from various studies on Rotarix had indicated that the vaccine is well tolerated and sufficiently safe to go on to the large-scale, phase III studies. Preliminary results from vaccine efficacy studies carried out in Latin America showed that two doses prevented nearly 85% of severe diarrheal disease caused by rotavirus: 92% of severe diarrheal disease caused by rotavirus serotype G1, and 80% of severe diarrheal disease caused by rotaviruses other than G1. In terms of reactogenicity the vaccine has not been 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. The phase III study of Rotarix is intended to address the risk of intussusception and to provide other information on the vaccine. Now starting up in 12 countries of Latin America, that study will include a population of 60 000 children and should be concluded in September 2004.

Merck's RotaTeq is a pentavalent live reassortant bovine-human RV that includes strains designated G1, G2, G3, G4, and P1 (1). The vaccine is administered orally in a three-dose regimen, beginning at the age of 2 months, with intervals of one to two months between doses.

Several clinical trials have suggested 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 (1). In a phase IIa proof-of-concept study the safety and efficacy of a quadrivalent vaccine (G1, G2, G3, and P1) were 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.

A study to assess the risk of intussusception or of other serious adverse events (SAEs) with RotaTeq was begun in 2001 (1). This large-scale phase III trial is called the Rotavirus Efficacy and Safety Trial (REST). In the REST study, infants who are 6 to 12 weeks old are enrolled to receive three doses of either vaccine or placebo orally at intervals of 4 to 10 weeks. The infants are actively followed for SAEs for at least 42 days after each dose. To ultimately declare safety with respect to intussusception, two 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 group of 10 000 subjects will be enrolled, and the incidence of intussusception among vaccine versus placebo recipients will be reevaluated after those subjects have completed dosing and follow-up.

As of early October 2003 more than 57 000 infants—in 11 countries around the world, including several in Latin America—had been enrolled in the REST study and had received at least one dose of either vaccine or placebo (1). Although several potential intussusception cases have occurred, the characteristics and timing of the cases with respect to vaccination suggest that these are background cases and not vaccine related. The incidence of potential cases observed is approximately 1 per 2 500 to 3 000 infant-years, and this incidence is similar to the projected background rate of 1 per 2 000 infant-years. No potential cases have been observed

within two weeks after any dose given in the REST study.

## **AREAS BESIDES VACCINES ALSO NEED WORK**

While the phase III trials that are now going on will yield important information on the potential benefits of new vaccines, additional knowledge is needed in other areas relating to rotavirus disease, according to the PAHO report (1).

One important subject is the economic impact of rotavirus disease and the cost-effectiveness of vaccination. Another concern is laboratory surveillance of rotavirus. Having information in those two areas will help each country in the Americas to take the most appropriate steps to prevent rotavirus infection and also to be in a position to decide on introducing a vaccine when one becomes available.

### **Economic aspects**

The economic aspects of rotavirus are important because of the burden that the disease imposes in terms of morbidity and mortality in children and costs to health systems, families, and society in general (1).

There are two types of economic analyses that are relevant to rotavirus: economic impact and economic evaluation of the cost-effectiveness of health interventions. With economic impact analyses, the social cost is calculated on the basis of epidemiological data and event costs. These data make it possible to estimate the cost for cohorts in a given year, the cost for families, and the burden on the health system. Cost-effectiveness considers the combination of the cost of vaccination and the resulting health benefits.

There are three broad types of costs: direct medical costs, other direct expenses, and indirect costs. Direct medical costs are ones that are associated with medical care, hospitalization, consultation, diagnostic tests, and treatment (paid by the health system and the family). Other direct expenses include ones incurred by the family in connection with hospital visits or in addition to medical costs, such as transportation. Indirect costs are expressed in terms of lost production by society in general as a result of parents and other caregivers having to be absent from work.

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 those events.

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

The benefit for a national vaccination program and a health system should be considered relative to the cost saved as a result of vaccination. Specific factors to assess include whether the medical costs saved are 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 what the relative costs are for different possible 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 terms of 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.

Various studies in the Americas have provided essential information to use in these economic analyses. For example, one study found that rotavirus is a significant cause of morbidity and mortality among Peruvian children (4). In their first 5 years of life, an estimated 1 in 1.6 children will experience an episode of rotavirus diarrhea, 1 in 9.4 will seek medical care, 1 in 19.7 will require hospitalization, and 1 in 375 will die of the disease. Per year, this represents approximately 384 000 cases, 64 000 clinic visits, 30 000 hospitalizations, and 1 600 deaths. The annual cost of medical care alone for these children is some US\$ 2.6 million, without taking into account the indirect or societal costs of the illness and the deaths. Rotavirus immunization provides the prospect of decreasing the morbidity and mortality from diarrhea in Peru, but a vaccine regimen would have to be relatively inexpensive, a few dollars or less per child, for there to be an overall cost savings.

Data on the disease burden have come from other research in Latin America as well (1). 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 nonbloody diarrhea in pediatric sentinel hospitals in Argentina, Chile, and Venezuela in children under 36 months of age. Based on the findings in those hospitals, the researchers estimated that each year there were 106 000 rotavirus-associated medical visits in Argentina, 48 000 visits in Chile, and 98 000 visits in Venezuela. The num-

bers of rotavirus-associated hospitalizations in those three countries were 21 000, 8 000, and 31 000, respectively.

### Surveillance considerations

Rotavirus includes a genetically diverse variety of strains, which are categorized into groups, subgroups, and serotypes (5). The prevalence of rotavirus strains varies geographically, and multiple strains may circulate concurrently.

Characterizing the most common rotavirus serotypes, so that they can be considered for inclusion in vaccines, is a high priority for surveillance (1). In addition, once vaccines have been introduced, 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.

Existing characterization methods, such as reverse transcriptase polymerase chain reaction for genotyping and monoclonal antibodies for serotyping, identify more than 95% of the circulating strains of rotavirus. With some other strains, molecular nucleotide sequencing methods and traditional virologic methods, such as neutralization with specific antisera, need to be used. These technologies should be available to all countries.

### RECOMMENDATIONS

A number of recommendations came out of the September meeting in Lima (1). Among the general suggestions were:

- Rotavirus epidemiological studies that have already been approved in the Region of the Americas 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 the ones that already exist for the surveillance of polio, measles, and rubella so that the results from the various studies on rotavirus in the Americas can be compared.
  - The methodology for conducting economic studies should be standardized so that they will be comparable.
  - Disease burden studies should be carried out as soon as possible in those countries that do not have them, to serve as a basis for taking the necessary preventive steps, including the probable introduction of a vaccine.
- Cost-benefit and cost-effectiveness studies are needed to help drive information-based policy decisions regarding the future introduction of RV vaccines.

The meeting also produced a number of recommendations regarding surveillance and laboratory procedures. According to the PAHO report (1), these included:

- The rotavirus laboratory network should be integrated into the network already established for the surveillance of polio in the Americas.
- In every case of acute diarrheal disease a stool sample of approximately 5 mL should be collected, preferably on the day that 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 °C to 8 °C and kept in this temperature range if they are going to be processed within seven days after they were collected. If the laboratory tests are going to be conducted within two months, it is recommended to store the samples at -20 °C. If they are going to be processed after two months, the samples should be kept at -70 °C. 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 enzyme-linked immunosorbent assay (ELISA) kits recommended in the rotavirus Generic Protocol of the World Health Organization.
- For genotyping the viruses, the reverse transcriptase polymerase chain reaction technique should be used.

Complete English- and Spanish-language copies of the PAHO report on the rotavirus meeting in Lima can be viewed and downloaded for free from the PAHO Web site (<http://www.paho.org>).

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### SINOPSIS

#### Reunión regional para las Américas evalúa el progreso contra los rotavirus

*La diarrea provocada por la infección por rotavirus es una de las principales causas de morbilidad y mortalidad en el mundo. Los rotavirus ocasionan un total de alrededor de*

111 millones de casos de diarrea y 440 000 muertes, 82% de ellas en países en desarrollo. Solo en la Región de las Américas, los rotavirus causan aproximadamente 75 000 ingresos hospitalarios y 15 000 muertes cada año. Con el objetivo de evaluar la marcha de la lucha contra los rotavirus en la Región, a principios de septiembre de 2003 se celebró en Lima, Perú, una reunión cuyos participantes examinaron la información epidemiológica, debatieron acerca de los adelantos alcanzados en el desarrollo de nuevas vacunas contra rotavirus y describieron sus experiencias con la vigilancia de la infección rotavírica. En los próximos años pueden aparecer en el mercado varias vacunas, entre ellas Rotarix (Glaxo-SmithKline) y RotaTeq (Merck). Ambas vacunas ya han pasado exitosamente por los estudios de fases I y II y en estos

momentos se llevan a cabo extensos estudios de fase III. No obstante, aún no se conoce lo suficiente acerca del impacto económico de la enfermedad, la efectividad en función del costo que pueda llegar a alcanzar la vacunación y la vigilancia de los rotavirus en el laboratorio. La reunión realizada en Lima generó varias recomendaciones, entre ellas algunas de carácter general acerca de los estudios epidemiológicos sobre rotavirus, la metodología de los estudios de corte económico y una base de datos para su vigilancia. En relación con los laboratorios y las técnicas analíticas, las recomendaciones se centraron en las redes de laboratorios, el mejor momento para recolectar las muestras de heces y la manera de almacenar y procesar esas muestras.

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### Conference on Health Promotion and Health Education

*Dates:* 26-30 April 2004  
*Location:* Melbourne Exhibition and Convention Centre  
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"Health2004" is the 18th World Conference on Health Promotion and Health Education. More than 2 000 delegates are expected to attend, representing governments, major international organizations and foundations, community groups, public health organizations, medical professionals, and others. The meeting is sponsored by the International Union for Health Promotion and Education, with support from the World Health Organization and other groups.

The program will include plenaries, policy forums, symposia, workshops, skill-development and discussion sessions, abstract-driven sessions, and formal and informal networking. The meeting will cover the entire range of health promotion and health education issues, with such subjects as cervical cancer screening, healthy aging, mental health, physical activity, multicultural health, health-promotion theory, safety promotion and injury prevention, tobacco control, and workplace health.

The registration fee is AUD\$ 1 375 (about US\$ 1 074) if paid after 15 February but before the meeting, and AUD\$ 1 495 (about US\$ 1 152) if paid at the conference.

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