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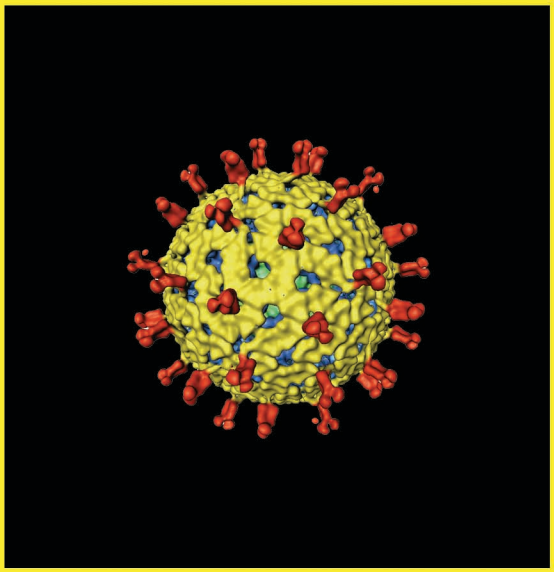

Epidemiological Surveillance of Diarrheal Diseases Due to Rotavirus Field Guide

Pan American Health Organization
Regional Office of the World Health Organization

Epidemiologic Surveillance of Diarrheal Diseases due to Rotavirus

Field Guide

Scientific and Technical Publication No. 623

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PAHO would also like to express its gratitude for the valuable contribution of ministry of health professionals from the countries who collaborated with staff from the Immunization Unit in the Family and Community Health Area to prepare this field guide.

ABOUT THE IMMUNIZATION FIELD GUIDES

The Expanded Program on Immunization is viewed as one of the most successful public health experiences in the Americas because it has played a pivotal role in reducing infant mortality from vaccine-preventable diseases in the Region. In fact, since the program was launched, our countries stopped the transmission of wild poliovirus in the Region in 1991 and interrupted indigenous measles transmission in November 2002; they also are making significant gains in the battle to eliminate rubella and congenital rubella syndrome. In addition, national immunization programs are undertaking extraordinary efforts to identify at-risk populations and overcome inequities in vaccination. To maintain these advances and to cope with new challenges, such as the introduction of new vaccines, partnerships will have to be strengthened among governments, donor agencies, the private sector, scientific associations, and society as a whole.

To this end, PAHO is promoting the best technical quality by issuing these practical field guides, that have been prepared by the Immunization Unit in the Family and Community Health Area. The most recent techniques presented in the field guides, coupled with useful illustrations, will help health workers in their efforts to control, eliminate, or eradicate diseases such as poliomyelitis, neonatal tetanus, yellow fever, diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b infections, hepatitis B, measles, and rubella. The field guides also include standardized methods and procedures for conducting epidemiologic surveillance and maintaining an up-to-date information system that makes it possible to take timely and effective decisions.

These field guides are based on the latest scientific information and they bring together the experience of prominent health professionals in the field. As a result, they are particularly suitable for promoting strategies that have already proven to be effective. The strengthening of prevention activities, the reduction of health inequities, and the promotion of technical expertise in vaccination services were the principles that guided the preparation of the guides.

The Expanded Program on Immunization, a joint effort of all the countries of the Americas, effectively contributes to the attainment of the Millennium Development Goals.

Mirta Roses Periago
Director
Pan American Health Organization

PREFACE

The high morbidity and mortality rates from rotavirus diarrheal diseases and the availability of new vaccines pose a challenge for the governments of the Region, which must decide to introduce the vaccine into their national programs, thus contributing to attainment of one of the Millennium Development Goals: by 2015, reduce mortality in children less than 5 years old by two-thirds. In this scenario, public health workers will face the task of providing decision-makers with information on the cost-effectiveness of introducing the vaccine into regular programs and on the expected impact of this intervention on the health of the population. The goal of this field guide is to furnish the basic guidelines for the surveillance of rotavirus disease—since epidemiologic surveillance is the basis for understanding the behavior of diseases in the phase prior to introducing a vaccine into national programs—and also, once the vaccine has been added to the routine series, to evaluate the effectiveness of the program and monitor adverse events supposedly attributable to vaccination or immunization (ESAVI). This field guide was prepared by the Pan American Health Organization, using the basic principles of the Generic Protocol for conducting surveillance of rotavirus infection of the WHO Department of Vaccines and Biologicals and with contributions from the countries of the Region, to help the health workers who will conduct the surveillance of this disease in the respective countries. The field guide covers clinical and epidemiological aspects, disease burden, laboratory procedures, steps for proper epidemiological investigation, and measures for the prevention and control of rotavirus disease.

1. INTRODUCTION

Rotavirus infection is responsible for some 600,000 deaths annually and approximately 40% of hospitalizations for diarrhea in children aged under 5 years worldwide; it is the leading cause of diarrhea in this population group. Rotavirus can cause an asymptomatic infection in infants aged under 3 months, and even symptoms of severe diarrhea with dehydration that can lead to death. The available data indicate that rotavirus is responsible for approximately 75,000 hospitalizations and nearly 15,000 deaths annually in the Region.

The incidence of rotavirus infection in developing countries is similar to that of developed countries, where neither water quality nor hygiene/sanitary conditions have been shown to have an effect in controlling the infection. However, case-fatality in the poorest countries is higher, due to malnutrition and barriers to accessing health services in a timely manner. In developing countries, the highest infection rates occur in children aged 3-11 months, while in developed countries infection rates peak in the second year of life.

In addition to the high social cost, the economic cost is significant, owing to the excessive demand placed on health care centers by the high morbidity. At present, efforts to develop a safe and effective vaccine have led to new vaccines entering the international market. Given the imminent possibility of introducing a new vaccine in national immunization programs, continuously updated information is needed on the behavior of the disease and the predominant serotypes circulating in countries of the Region.

2. EPIDEMIOLOGY

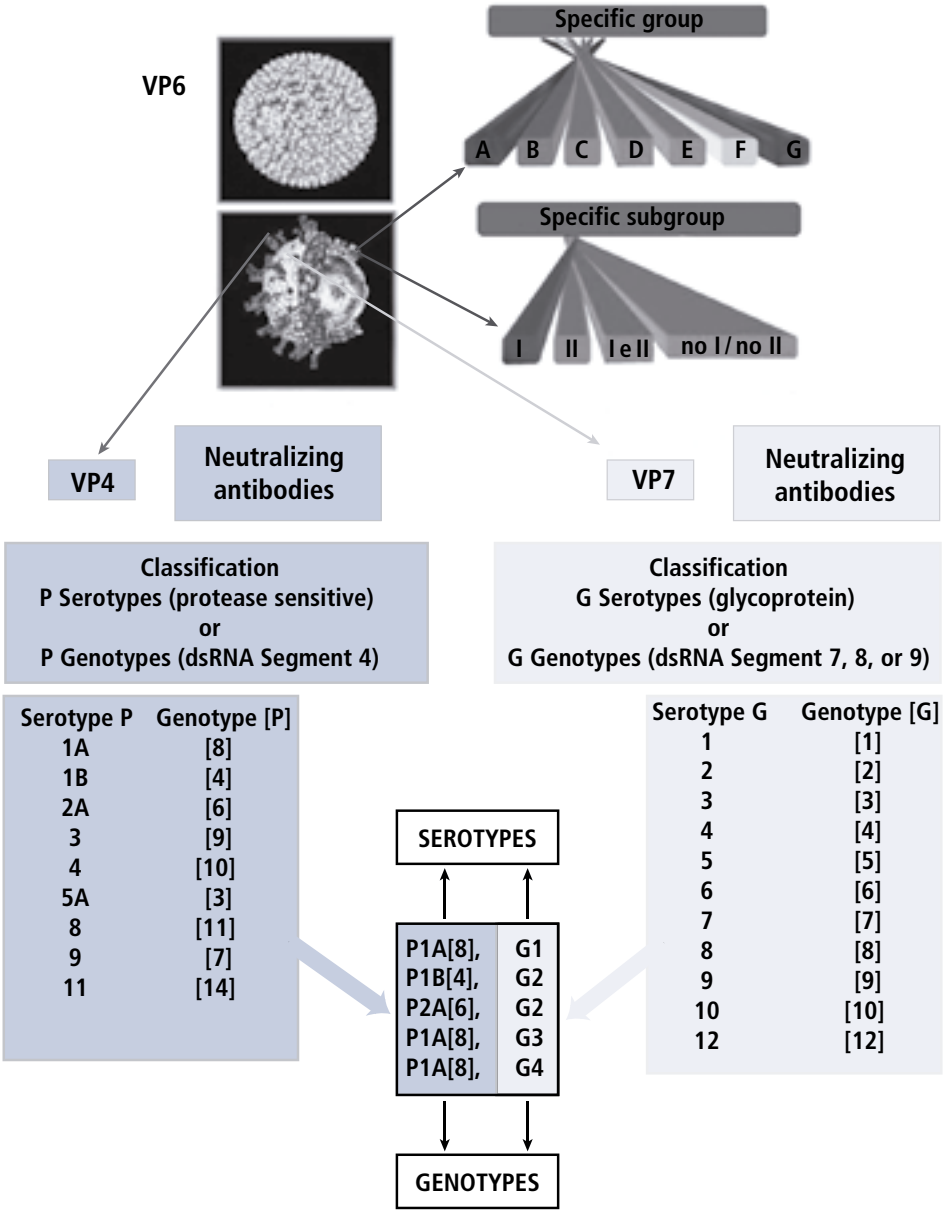
2.1 Infectious Agent

The genus rotavirus belongs to the *Reoviridae* family. It is a double-stranded ribonucleic acid (RNA) virus with 11 segments. Seven principal rotavirus groups have been identified, labeled A through G. However, only the A, B, and C groups infect humans, and the A group is the most important.

The viral particle is wheel-shaped and consists of three concentric layers of protein around the genome (Figure 1). The outside protein layer of the virus particulate consists of two superficial viral proteins: VP4 and VP7. Rotavirus classification by serotype is based on the antigenic specifications of these two proteins. Both the VP7 (type G for glycoprotein) and VP4 (type P for protease sensitivity) protein elicit the production of neutralizing antibodies and are involved with protective immunity. There are 15 G serotypes and 14 P serotypes. In the G serotypes, a precise correlation can be made between serotype and genotype. However, such a correlation is not

found in the P serotypes. There are 20 P genotypes, always numbered 1 to 20 in brackets: for example P[4]. The genes coding the G and P antigens are added independently, allowing various combinations of G and P to be observed.

Figure 1. Rotavirus Structure



Source: Adapted from the presentation "Laboratory Diagnosis and Molecular Epidemiology of Rotavirus in the Americas." Leite JPG, Department of Virology, Fiocruz, Ministry of Health, Brazil. Presented during the International Workshop on Rotavirus Surveillance. Rio de Janeiro, 12-16 December 2005.

Four strains are predominant worldwide (including Latin America): G1P[8], which is responsible for the majority of infections; G2P[4]; G3P[8]; and G4P[8]. In addition to these four, others have been described with serotypes G5, G8, and G9. Serotype G9 is considered to be the world's 5th most important serotype.

2.2 Transmission

The precise transmission mechanisms are still under investigation, but direct fecal-oral contact is considered the most significant. The evidence also points to propagation by saliva droplets and secretions from the respiratory tract.

The virus is highly infectious and very stable in the environment: it can survive for hours on hands and even days on hard surfaces, and it remains stable and infectious in human stool for up to 1 week. Individuals with rotavirus excrete significant quantities of viral particles before they begin showing symptoms of the disease, throughout the course of the diarrhea, and, in one-third of the cases, up to 1 week after the symptoms disappear. Many people excrete the virus without experiencing diarrhea.

Person-to-person transmission through the hands appears to be responsible for the virus spreading in closed environments, such as homes and hospitals. Transmission between children in day-care centers is caused by direct contact and through contaminated food and/or toys.

Stools generally contain 100 billion viral particles per milliliter, and the infectious dose is between 10,000 and 10 million viral particles. Although rotavirus has been identified in several species of animals, both wild and domestic, animals do not appear to play a significant role as reservoirs or in transmission to human beings.

2.3 Incubation

The incubation period is generally 24-48 hours.

2.4 Immunity

An initial infection induces a local and systemic immune response to the serotype responsible for the infection (homotypic immunity) as well as to a high percentage of other serotypes (heterotypic immunity). Thus, after an initial infection, 88% of children are protected against severe infection. After a second infection, 100% have developed immunity against severe infection, and the majority against any rotavirus disease.

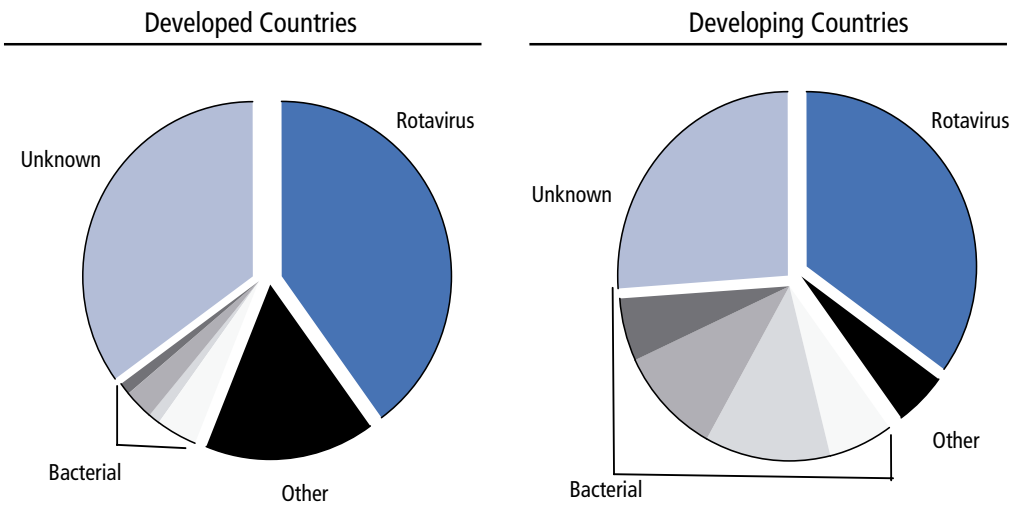
In developing countries, 65%-80% of children have rotavirus antibodies by the age of 12 months, and 95% by the age of 24 months. Thus, the incidence of symptomatic illness declines rapidly after 24 months of age, and repeated infections may be asymptomatic or accompanied by mild symptoms.

In general, infants aged under 3 months with rotavirus infections are asymptomatic, while those infected for the first time after that age generally show symptoms. The explanation for this finding is not entirely clear, but appears to be linked to the presence of maternal antibodies.

2.5 Distribution

The distribution of this viral disease is universal. The incidence of rotavirus diarrhea is similar in developed and developing countries alike, where roughly one-third of severe gastroenteritis cases are attributable to rotavirus (see Figure 2). Improvements in the environment impacting the quality of water or food conditions have little probability of changing the incidence of the infection.

Figure 2. Causes of Severe Gastroenteritis in Children



Source: Kapikian AZ, Channock RM. Rotaviruses. In: *Fields Virology*, 3rd ed. Philadelphia, PA: Lippincott-Raven; 1996:1659. With authorization from Lippincott Williams & Wilkins.

2.6 Epidemiology of the Disease

In temperate climates, infections occur predominantly in winter, while in tropical climates, cases generally occur year-round, although seasonal peaks may occur in winter. As a result, an infant born in a temperate country after the winter season will not be exposed to the virus until the following year, but those born in a tropical country will be exposed to the virus year-round. Thus, the average age of onset of infection is younger in tropical countries, where children get sick in the first year of life,

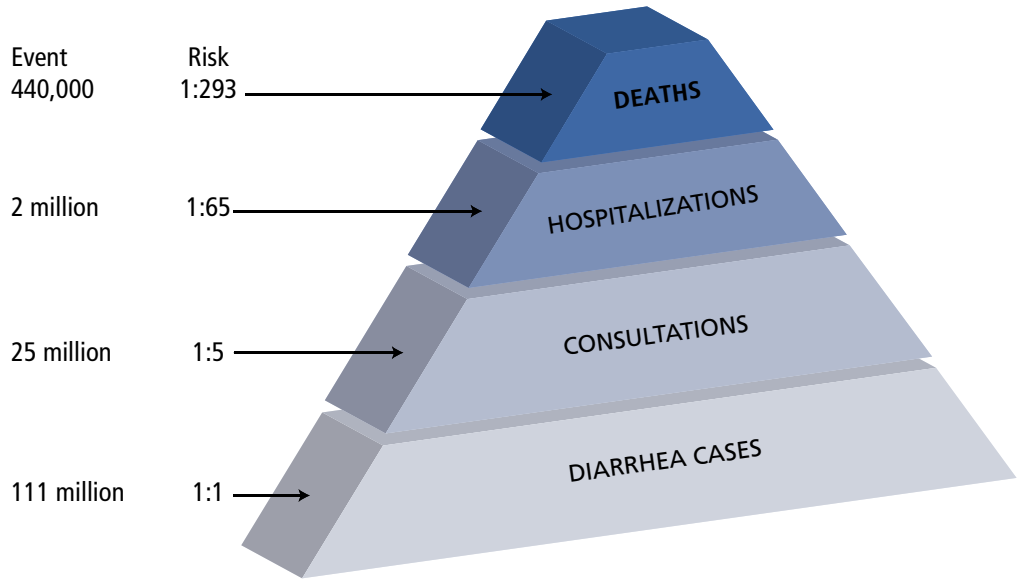
compared to the average for those dwelling in temperate countries, where 2- to 3-year-olds tend to become infected.

2.7 Disease Burden

Almost half a million children in developing countries die each year from rotavirus infections. Mortality is extremely high in these countries, due to a combination of factors, including limited access to health services (rehydration therapy) and high levels of malnutrition.

According to Parashar et al. (2003), between 1986 and 2000, each year rotavirus caused 111 million episodes of infantile diarrhea requiring home care only worldwide, 25 million medical visits, 2 million hospitalizations, and an average of 440,000 deaths (Figure 3). Thus, by 5 years of age, almost all children have experienced an episode of rotavirus diarrhea: 1 out of 5 children has been brought in for medical consultation, 1 out of 65 has been hospitalized, and 1 out of about 293 has died. A more recent study by the same authors (Parashar et al. 2006) estimates that from 2000-2004, child deaths from rotavirus rose to 600,000 or more around the world. In Latin America, each year an estimated 10 million children suffer from the disease, 2 million are brought in for medical consultation, 75,000 must be hospitalized, and 15,000 die.

Figure 3. Overall Burden of Rotavirus Diarrhea, 1986-2000



Source: Parashar UD, et al. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis.* 2003;9(5):565-72.

2.8 Economic Studies

Health economics research should be conducted to help policymakers understand and weigh the options of introducing a vaccine or expanding the age group receiving vaccines already used in the country. Cost studies can help measure the economic burden of a vaccine-preventable disease to society.

In terms of rotavirus, the economic impact of the burden of disease and mortality is significant for health systems, the family, and society as a whole. The direct cost of care must be considered, including hospitalization, medical visits, diagnostic tests, and treatment, whether paid for by the health system, the family, or both. Other direct costs include the family's expenses for hospital visits, such as transportation, food, and lodging costs. Indirect costs can also be measured in terms of productivity losses due to absenteeism and immeasurable social costs.

Studies are also needed to help estimate the cost of establishing a vaccination program and evaluating the medium- and long-term availability of funding to ensure a program's financial sustainability. Conducting this second evaluation before introducing a vaccine is a critical component in the decision-making process of national immunization programs.

3. CLINICAL ASPECTS

3.1 Pathogenesis

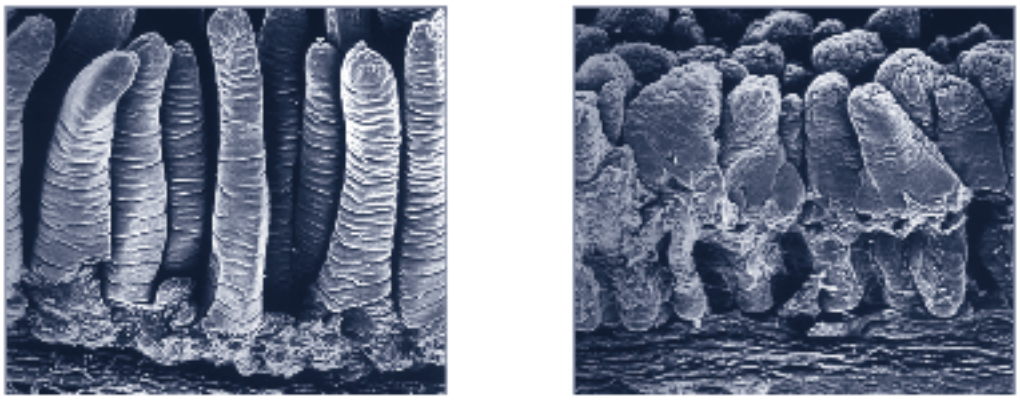
Rotavirus can adhere to the epithelial lining of the gastrointestinal tract. The main site of virus replication is on the mature enterocytes on the villi in the upper small intestine, but rotavirus also spreads to the ileum. Lesions in the mucous membrane are caused by the selective destruction of the ends of the intestinal villi.

Figure 4 shows an electronic micrograph of the intestinal villi of an uninfected (Normal) and a rotavirus infected (Abnormal) animal model, where destruction of the villi responsible for absorption can be observed.

For this reason, the principal mechanism causing rotavirus diarrhea is reduced absorption of salt, glucose, and water due to intestinal damage, and the replacement of epithelial absorptive cells by secretory cells of the villi crypts. Symptoms last proportionally to the severity of the damage.

Finally, there is evidence of another mechanism that causes diarrhea through the action of a nonstructural rotavirus glycoprotein (NSP4) as a viral enterotoxin. This glycoprotein leads to increased calcium levels and induces secretory diarrhea, similar to bacterial intestinal infections such as shigellosis and cholera.

Figure 4. Intestinal Villi: Normal and Altered by Rotavirus Action



Normal Abnormal

Source: Courtesy of Dr. Graham Hall, Berkshire, UK for Zuckerman et al, eds. *Principles and Practice of Clinical Virology*, 2nd ed. London: John Wiley & Sons; 1990:182.

3.2 Clinical Characteristics

Vomiting begins early in the course of the disease and is followed by watery diarrhea, which can be mild and of short duration, or severe, with secondary dehydration from gastrointestinal fluid loss. Fever and abdominal pain are frequent. Vomiting and fever lessen 2 to 3 days after onset of the disease, and diarrhea tends to persist for 4 or 5 days. Infections tend to be more severe in infants 3-24 months old.

As mentioned earlier, children infected with rotavirus during the first 3 months of life tend to be asymptomatic, probably due to maternal antibodies. Also, individuals with repeated infections may be asymptomatic or exhibit mild symptoms due to the immunity acquired from previous infections.

3.3 Differential Diagnosis

Symptoms may be similar to those of other infectious agents that cause watery diarrhea in infants, such as: enteric adenovirus, astrovirus, calicivirus, *Shigella*, *Salmonella*, enterotoxigenic *Escherichia coli*, *Vibrio cholerae*, *Campylobacter jejuni*, *Staphylococcus aureus,* and fungi, such as *Isospora belli*, more common in immunosuppressed individuals. The most common parasites that cause diarrhea are *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium*.

3.4 Complications

The main complication is severe dehydration, which can lead to shock and even death.

3.5 Treatment

Treatment consists of replenishing lost fluids. When vomiting and diarrhea are severe, oral rehydration therapy is necessary and, in the severest cases, intravenous rehydration. Antibiotic use is inappropriate.

The first step is to determine the degree of dehydration, based on the signs presented, and then to select the most appropriate treatment. The child should be evaluated and treated according to the rules and plans for the prevention and management of diarrheal diseases, available in PAHO's IMCI (Integrated Management of Childhood Illness) manuals:

Plan A is for cases with no signs of dehydration. It recommends giving the child more fluids than usual and sufficient nutrition to prevent dehydration and malnutrition; it is advisable to take the child to a health center if after 3 days, there is no sign of improvement or there are severe signs such as repeated vomiting, fever, numerous bouts of diarrhea, or resistance to eating or drinking.

Plan B calls for oral rehydration therapy initiated in the local health center and then continued at home.

Plan C is for the most serious cases—when the child drinks little or is incapable of drinking, has sunken eyes, extremely dry mucous, or is lethargic or unconscious—and intravenous rehydration is needed.

4. EPIDEMIOLOGIC SURVEILLANCE

Epidemiologic surveillance, as defined by Alexander Langmuir in 1963, is the ongoing observation of the distribution and trends in the incidence of diseases through the systematic collection, compilation, and analysis of morbidity and mortality report as well as other relevant data, and dissemination of that information to all who need to know. The data obtained through such surveillance and its analysis and interpretation should guide decisions about control measures.

4.1 Objectives of Surveillance of Rotavirus Diarrheal Diseases

1. To understand the epidemiology of diarrheal diseases
2. To have data to evaluate the morbidity and mortality burden of the disease
3. To apply the necessary control measures
4. To evaluate the impact of the vaccine when introduced

4.2 Case Definition

4.2.1 Suspect Case

Every child aged under 5 years hospitalized for acute diarrhea.

Definition includes:

- **Child age under 5 years:** Every child from 0 to 4 years, 11 months, and 29 days.
- **Hospitalized:** Child is admitted to the rehydration room or the hospital ward. In hospitals with no rehydration room, all children who receive oral or parenteral rehydration in the hospital environment are considered hospitalized, even if not officially admitted to the hospital ward.
- **Acute diarrhea:** Three or more liquid or semi-liquid evacuations within 24 hours, lasting for up to 14 days.

Although stool consistency is more important than the number of evacuations, it is important to bear in mind that children who are exclusively breast-fed tend to have watery stools.

The following criteria are excluded:

- Children aged over 5 years or older
- Prolonged diarrhea (lasting >14 days)
- Hospitalization for another reason, although diarrhea present
- Stool sample collected more than 48 hours after hospital admission, due to the risk of it being a hospital infection
- Referral to sentinel hospital from another health center, where patient had been hospitalized more than 24 hours earlier for symptoms of the current case of diarrhea

4.2.2 Confirmed Case

Suspect case for which there is a timely stool sample and the lab results are positive for rotavirus. Outbreaks are confirmed when an epidemiological link is established with a laboratory-confirmed case.

4.2.3 Inadequately Investigated Case

Suspect case in which test results were not available and no epidemiological link has been established with a laboratory-confirmed case in outbreaks.

4.2.4 Discarded Case

Suspect case with a timely stool sample in which the lab result is negative for rotavirus.

Timely is defined as a stool sample collected within 48 hours of admission to the hospital.

4.3 Surveillance Strategies

4.3.1 Type of Surveillance

It is recommended that rotavirus diarrhea surveillance be conducted through hospital sentinel units. Although this method has certain limitations from the standpoint of population representativeness, essential data can be obtained at lower cost, making it possible to identify situations of risk.

Prioritizing surveillance of hospitalized cases is justified for the following reasons:

1. Hospitalizations due to severe diarrheal disease are relatively common with this disease.
2. Hospitalizations are easy to detect. In places where the majority of children with severe cases of rotavirus diarrhea are likely to be treated in hospitals, case-finding will be easier and require fewer resources than if conducted in the community at large.
3. Hospitalizations represent a significant cost in terms of health resources. This surveillance can help determine the economic burden of the disease.
4. Hospitals have laboratory services, which facilitate the collection, storage, transportation, and processing of samples to determine the presence of rotavirus and confirm suspect cases.
5. This surveillance method makes it possible to monitor intestinal invagination.

4.3.2 Selection Criteria for Sentinel Hospitals

The following technical and operational criteria are recommended:

1. Prioritize hospitals with a demographically and geographically defined population.
2. The sentinel hospital should be accessible geographically, economically, and organizationally.
3. The sentinel hospital should be representative of the target population for surveillance, that is, of children aged under 5 years.
4. In order to have a sufficient number of hospitalizations for rotavirus, for each sentinel hospital the average number of admissions for diarrhea per year should be at least 250-500 children aged under 5 years. Based on a moderate calculation that 30% of severe diarrhea cases will be attributable to rotavirus, 75-150 cases of rotavirus should be expected each year.
5. The sentinel hospital should have the capacity to collect and store samples.

6. The sentinel hospital should conduct rotavirus screening through methods of rapid antigen detection or have a reliable system to transport samples to a reference laboratory.
7. The hospital should have the human and logistical resources necessary for getting the sentinel surveillance system up and running.
8. Institutional commitment is needed.

4.3.3 Operational Structure of the Surveillance System

General coordinator

The national coordinator of the epidemiologic surveillance system for rotavirus diarrheal diseases will have the following duties and responsibilities:

- Monitors the activities in each sentinel hospital, identifying potential problems and supporting the search for solutions;
- Follows up and periodically evaluates the data obtained;
- Ensures that all information generated in the country's sentinel hospitals is consolidated and analyzed;
- Prepares national reports;
- Provides feedback to the country's sentinel hospital network; and
- Disseminates information monthly through PAHO.

Laboratory manager

- Serves as the national technical reference for laboratory diagnosis of rotavirus diarrheal diseases;
- Oversees laboratory supplies to maintain a regular supply so as not to interrupt surveillance;
- Coordinates with hospital laboratories to ensure the proper flow of samples;
- Evaluates the activities and data along with the individuals responsible for the surveillance;
- Conducts quality control for laboratories at the sentinel hospitals that process samples for rotavirus diagnosis; and
- Conducts the confirmatory tests and typing of rotavirus on positive samples.

Sentinel hospital team

It is suggested that each team include an epidemiologist or person responsible for information, a person from the local laboratory, and a person from the clinical area, with the following duties and responsibilities:

Epidemiologist or person responsible for information:

- Collects the data generated in the clinical area (hospital records) and the laboratory;
- Enters the data into a specifically designed database;
- Inputs lab results into the database;
- Consolidates the data on suspect cases recorded in the system on the first day of each month;
- Analyzes the data monthly, including evaluation of surveillance indicators;
- Prepares monthly reports;
- Provides monthly feedback to the hospital team; and
- Sends the local report to the general coordinator of the country's epidemiologic surveillance system for rotavirus diarrheal diseases before day 5 of each month.

Team member from the laboratory:

- Receives stool samples;
- Properly stores the samples;
- Performs diagnostic test in a timely fashion or guarantees adequate transportation to the reference laboratory;
- Reports test results to the epidemiologist or person responsible for information;
- Sends the positive and undetermined samples, as well as 10% of the negative ones, to the country's central reference laboratory for quality control; and
- Obtains the results from those samples and reports to the team.

Team member responsible for the clinical area:

- Trains hospital personnel from different shifts to participate in surveillance;
- Ensures the proper collection of stool samples;
- Monitors the timely and adequate capture of data from eligible patients; and
- Monitors the participation of the hospital's clinical staff.

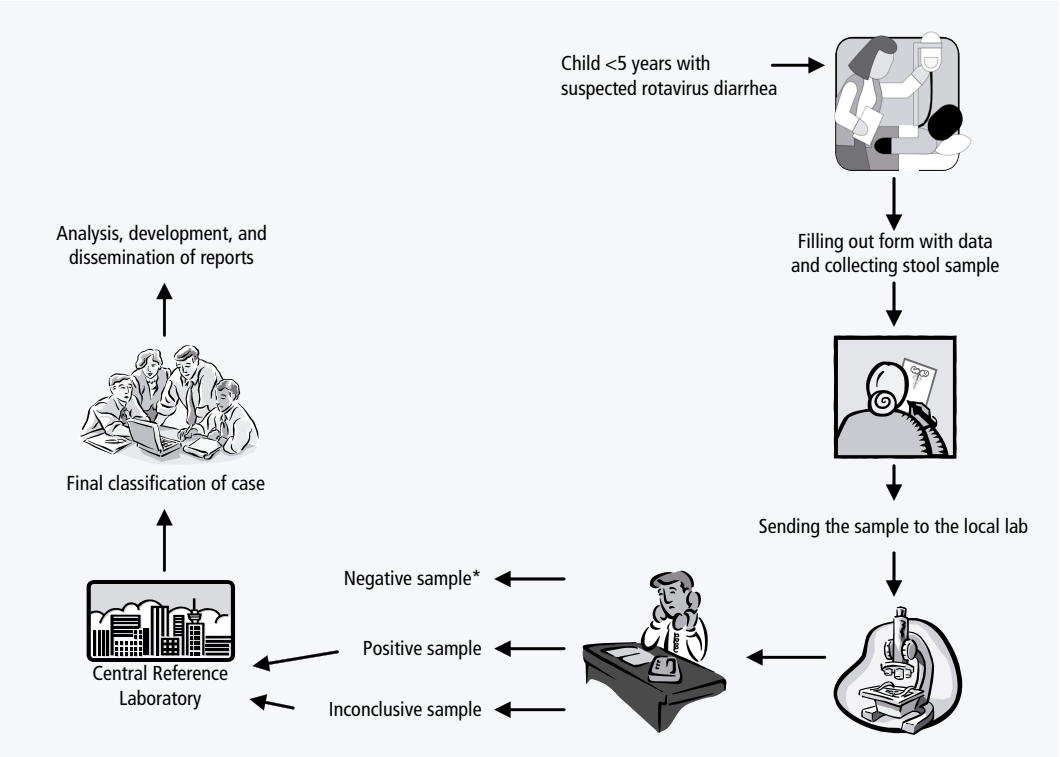
Each hospital team should prepare a monthly report with the surveillance data. This should be sent to the hospital's director and the general coordinator of the surveillance system for rotavirus diarrheal disease. In addition, weaknesses in surveillance should be discussed, doubts cleared up, and needed changes proposed to ensure sound operation of the surveillance system in place.

4.4 Surveillance Procedures

For each suspect case admitted to the sentinel hospital, the following steps should be taken (Figure 5):

- Complete the epidemiological investigation form. This form is completed when the patient is admitted to the hospital and on discharge (Annex 1: Rotavirus Diarrhea Reporting and Investigation Form).
- Enter the case in the respective database. Make a back-up copy at the end of every work day.
- Obtain a 5- to 10-ml stool sample during the first contact with the patient and send it immediately to the hospital laboratory.
- Record on the investigation form the number of days hospitalized for treatment of diarrhea, because the child may have been hospitalized for a longer period for another cause. Recording the number of days hospitalized for diarrhea treatment will help in calculating the disease burden.
- Record on the investigation form the number of days hospitalized in the intensive care unit, when applicable.

Figure 5. Sentinel Hospital Procedures for Surveillance of Rotavirus Diarrhea



*At least 10% of the negative samples (when total number of samples exceeds 100) should be sent to the Central Reference Laboratory for quality control.

— Classify the case as soon as the lab results are available, confirming or ruling out rotavirus infection.
— Ensure a continuous flow of updated data, adhering to the procedures established by the surveillance system.
— Consolidate and analyze data, according to Section 4.6 of this field guide.
— Prepare and disseminate the reports for the entire surveillance network.

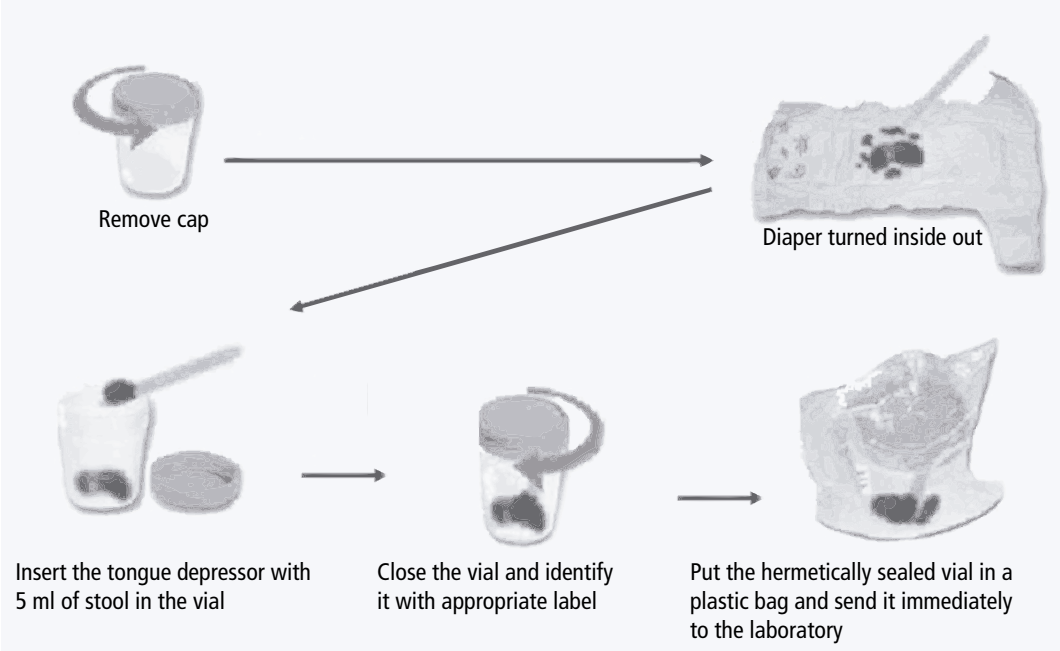
4.5 Laboratory Diagnosis

4.5.1 Sample Collection

A stool sample must be obtained from all suspect cases during the first contact with the patient. The sample should be collected within 48 hours of admission to the hospital. The following steps should be taken:

1. Collect 5-10 ml of stool (approximately the size of a thumb) and place in a vial using a spatula or disposable tongue depressor. Stimulate the anal sphincter of children aged under 1 year with a sterile swab and wait for an evacuation, placing a disposable diaper inside out so that the sample is not absorbed (Figure 6).

Figure 6. Collection of Stool Samples for Suspect Cases of Rotavirus Diarrhea



Source: Ministry of Public Health and Social Welfare of Paraguay. General Bureau of Health Surveillance. Project for surveillance of rotavirus diarrhea in children under 5 in Paraguay. Operating Manual. Asunción: PAHO/WHO; 2004:57.

2. Once the stool sample is collected, place it in a clean, screw-top vial bearing a label with the name of the case, the date, and the name of the hospital. Place the vial in a small individual plastic bag to avoid accidental spillage of the material.
3. Send immediately to the laboratory, attaching the forms indicated in the hospital norms.

4.5.2 Sample Storage and Transportation

- A sample can be stored up to a maximum of 7 days in a refrigerator set at between 2° C and 8° C, prior to shipment to the reference laboratory.
- In the reference laboratory, it is recommended that each sample be immediately divided into three vials, each with one-third of the sample. One vial should be stored at a temperature between 2° and 8° C, and the other two in a freezer at -20° C, until the time for confirmation and typing tests. Three drops of glycerol should be added to each vial and mixed gently before putting in freezer.
- Freezing/thawing/freezing cycles should be avoided to ensure the viability of the virus in the frozen material.
- In the case of storage for more than 4 months, a temperature of -70° C is recommended.

Considering the number of tests available in the commercial kits used to perform enzyme-linked immunosorbent assay, the laboratory can expect to obtain a large number of samples for processing. This is feasible, because to start therapy for rotavirus diarrhea, it is not necessary to wait for the results of lab tests.

For cases in which the presence of bacterial or parasitic enteropathogens needs to be determined, the specific standards for collection, management, and analysis of samples should be obtained from other sources.

4.5.3 Methods for Detecting Rotavirus

Several methods are currently available for detecting rotavirus, including enzyme-linked immunosorbent assay, polyacrylamide gel electrophoresis (PAGE), and reverse transcriptase-polymerase chain reaction (RT-PCR). The characteristic wheel-shaped appearance of the virus can be identified by electron microscopy. The method most recommended is the ELISA enzymatic immunoassay, as it is quick, sensitive, and less expensive.

Rotavirus can generally be detected in stool samples by an enzymatic immunoassay test up to 1 week after infection. Using ELISA, viral antigens (VP6 capsid protein)

can be identified in stool samples. Diluted samples are exposed to anti-VP6 antibodies fixed to a solid support. In cases where the sample contains rotavirus viral particles, these will react with the antibody and form a complex, which will subsequently be revealed through enzymatic color reaction. The intensity of the color can be measured by spectrophotometer absorbance and is directly proportional to the quantity of viral antigens present in the sample.

4.5.4 Interpreting Laboratory Results

In all positive cases, a fraction of the samples should be sent to the country's central reference laboratory for a confirmation test and typing of the virus. For undetermined cases, the test should be repeated by the country's central reference laboratory; if it is confirmed positive, the flow for positive samples will be followed.

In the case of negative results, the test need not be repeated and the case will be considered discarded. However, it is recommended that the local laboratory be asked to send at least 10% of negative samples to the country's central reference laboratory for quality control tests. Figure 5 shows the flow of laboratory results.

4.6 Data Analysis

It is important to analyze the data periodically in order to understand the characteristics of the disease and monitor the surveillance system. Suspect and confirmed cases should be described according to the time and epidemiological week of the onset of diarrhea and in a consolidated monthly analysis by age of the children and place where the cases occurred. It should also be established whether the case is an isolated occurrence or an outbreak has occurred in a day-care center, other institution, or the community.

Thus, the following data should be collected weekly and consolidated monthly:

- Number of hospitalizations of children aged under 5 years for any cause (a).
- Number of hospitalizations of children aged under 5 years for diarrhea (b).
- Number of hospitalized cases in which rotavirus diarrhea is suspected (c).
- Number of cases of suspect rotavirus diarrhea in which stool samples were taken in a timely manner (d).
- Number of suspect rotavirus diarrhea cases with epidemiologic report (e).
- Number of suspect rotavirus diarrhea cases with epidemiologic report and stool samples collected on a timely basis (f).
- Number of confirmed cases of children aged under 5 years hospitalized for rotavirus diarrhea (g).
- Number of samples testing positive for rotavirus with epidemiologic reports (h).

— Number of days of hospitalization needed to treat confirmed cases of rotavirus diarrhea (i).

— Average number of days of hospitalization needed for treating confirmed cases of rotavirus diarrhea—that is, total number of days of hospitalization to treat confirmed cases of rotavirus diarrhea divided by the number of confirmed cases of hospitalization for rotavirus diarrheal diseases (sum of i/g).

Based on the entry/consolidation of these data, the following indicators can be calculated:
• Percentage of hospitalizations for diarrhea in total hospitalizations of children aged under 5 years (b/a x 100).
• Percentage of suspect cases of rotavirus diarrhea with timely stool samples and epidemiologic reports (f/c x 100).
• Percentage of confirmed cases of rotavirus diarrhea in children aged under 5 years in cases hospitalized for diarrhea (g/c).
• Percentage of confirmed cases of rotavirus diarrhea in children aged under 5 years in suspect cases with samples and completed reports (g/f x 100).

Finally, after arriving at these indicators, others can also be calculated that are relevant in the surveillance of the disease. Annex 2 presents a form for monthly consolidation of such data.

4.7 Outbreak Investigation

An outbreak is suspected when the number of cases of rotavirus diarrhea at an institution or locality increases. First, through systematic data analysis, it is necessary to know the number of cases that generally occur. Infection in adults is usually subclinical, although outbreaks with clinical manifestations have been detected in geriatric centers.

When an outbreak of rotavirus is suspected, the following steps should be taken:

— Put together a field research team;

— Do a preliminary study of the available data before beginning the investigation;

— Tailor the definition of suspect cases to investigate to the preliminary analysis;

— If necessary, adapt the investigation form for rotavirus diarrhea cases to the definition established;

— Provide the team with all the technical and material conditions needed for collecting data and stool samples and storing and transporting samples to the laboratory;

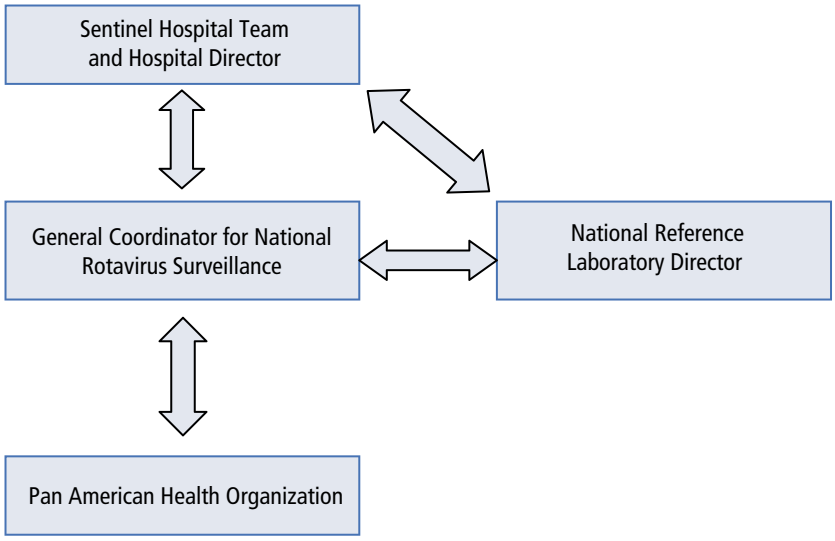
- Collect all epidemiological data on the suspect cases in the case investigation form;
- If the outbreak occurs in a single institution (day-care center, geriatric center, or hospital) or a single locality, take samples from 5 to 10 suspect cases in order to characterize the etiology of the outbreak. Other cases can be confirmed by epidemiological link;
- Process and send the stool samples to the appropriate laboratory, adhering to the standards outlined in Section 4.5.1 (Sample Collection) and 4.5.2 (Sample Storage and Transportation) of this field guide;
- Analyze the data for time, place, and individual, and verify if suspect cases are related;
- Formulate more specific hypotheses;
- Base control measures on the data analysis;
- Prepare a preliminary report with the field investigation data; and
- Once the laboratory test results are in, prepare the final report on the outbreak and distribute it to the respective entities.

The field investigation team needs to understand the disease and all procedures for sample collection, storage, and transportation, in addition to the general guidelines for the control of diarrheal diseases needed to inform the people at the location.

4.8 Information Flow

Figure 7 shows the information flow for rotavirus diarrhea cases.

Figure 7. Information Flow for Rotavirus Diarrhea Cases



5. PREVENTION AND CONTROL MEASURES

5.1 General Measures

- Since the virus tends to spread through contaminated hands, all family members and personnel at health and day-care centers should wash their hands after cleaning a child who has defecated, after disposing of the child's stool, after defecating, before preparing food, before eating, and before feeding a child.
- It is important for family members and personnel at health and day-care centers to collect the stools quickly from children and infants and wrap them in a sheet of newspaper or dispose of them in the latrine. It is also recommended that toys handled by the child be washed, given the risk that they may have been in contact with the child's mouth and thus be contaminated.
- Drinking water should be taken from the cleanest available source and boiled.
- All families should have a clean latrine or be encouraged to defecate far from the house at a location that is always more than 10 meters from the source of drinking water.
- Exclusive breast-feeding is highly recommended to decrease exposure to the virus.

Although improvements in hygiene, water supply, and wastewater elimination are all measures that can help to reduce severe episodes of diarrhea, comparable incidences of rotavirus disease in developed and developing countries indicate that the disease cannot be controlled exclusively with such measures.

5.2 Rotavirus Vaccines

In August 1998 the United States authorized a tetravalent vaccine prepared from human and rhesus strains (RRT-TV, RotashieldR, Wyeth Laboratories, Inc., USA), recommended for vaccinations of 2-, 4-, and 6-month-old infants. Several months later, after more than 1 million doses of the vaccine had been used, the VAERS (Vaccine Adverse Event Reporting System) detected a higher number of cases of pediatric intestinal invagination than expected the week after the vaccine was administered. As a result, in July 1999 the Centers for Disease Control and Prevention (CDC) suspended the use of the vaccine, which was immediately removed from the national vaccination schedule.

There is controversy over the precise degree of risk of intussusception presented by this vaccine, but it seems to be limited to the 2-week period immediately following administration of the first two doses and not more than 3-7 days after the first

dose. According to the CDC, the risk ranges from 1 in 4,600 vaccinated children to 1 in 11,000.

Two new vaccines currently on the market have been shown to be effective against severe rotavirus diarrhea. Both are composed of live attenuated viruses and are administered to infants orally in multiple doses. Studies evaluating the safety of these vaccines have not proven that vaccinated children are at greater risk of intestinal invagination than unvaccinated children.

As occurs with the natural rotavirus infection, these vaccines are expected to confer partial immunity after one dose and greater coverage with subsequent doses, and to be safe and effective in preventing acute disease. Table 1 summarizes the data on the two vaccines.

5.3 Outbreak Control

It is not necessary to isolate a person with rotavirus diarrhea or to bar children from day-care centers. However, as long as the excretion and spread of the virus persist—usually until the eighth day of infection—direct contact should be avoided between infants/children and individuals suffering from acute gastroenteritis, including infected family members and/or institutional caregivers (day-care centers and hospitals). Thus, it is important to employ careful hygiene and sanitary practices, including:

Table 1. New Rotavirus Vaccines

	GlaxoSmithKline (GSK)	Merck
Origin/composition	Human, monovalent Strain G1P[8]	Human-bovine, pentavalent Strains G1, G2, G3, G4, P[8]
Presentation	Lyophilized	Liquid
Administration	Oral	Oral
Storage temperature	2 to 8º C	2 to 8º C
Dosage	2 doses	3 doses
Efficacy against severe diarrhea*	85% (P: 0.001) (95% CI = 72-92)	98% (95% CI = 88-100)
Efficacy against hospitalization	85% (P: 0.001) (95% CI = 70-94)	95% (95% CI = 91-97)
Intestinal intussusception	No increase in incidence of cases after any dose of vaccine	No increase in incidence of cases in periods immediately after vaccination

* Data cannot be compared. Different methods were used for evaluating degree of severity.

Source: Adaptation. Ruiz-Palacios GM, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis; and Vesikari T, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N. Engl J Med*, 2006;354(1):11-33.

1. People responsible for the care of infants or the elderly should wash their hands frequently.
2. Drinking water should be protected from possible sources of infection and, in all cases, water should be boiled before drinking.
3. It has been shown that at children's day-care centers, placing a protective layer (for example, a plastic cloth) inside diapers can keep stools from leaking out, helping reduce transmission of the infection.
4. Passive immunization through the oral administration of specific immunoglobulin, when feasible, can offer greater protection to immunodeficient children or newborns with low birth weight.
5. Breast milk can also help protect against infection and reduce the intensity of diarrhea.

6. MONITORING INTESTINAL INVAGINATION

Given what happened with the RotashieldR vaccine, WHO recommends that special attention be given to monitoring all cases of severe adverse events—particularly intestinal invagination or intussusception—recorded after administration of the vaccine.

However, since the incidence of intestinal invagination varies from country to country and even from city to city in a single country, it is recommended that monitoring of intestinal invagination begin for children aged under 1 year, to create a database prior to introducing a new rotavirus vaccine. This will make it possible to identify and evaluate any additional risk that might be attributable to the vaccine.

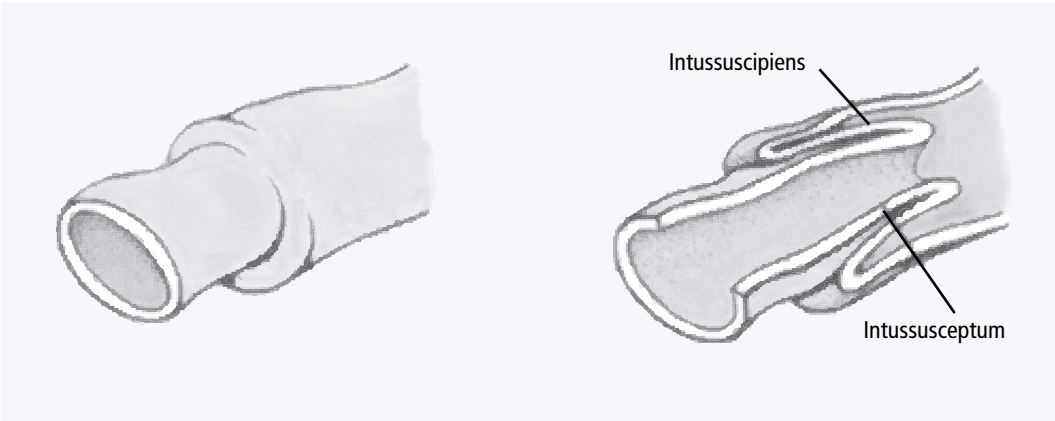
6.1 Clinical Aspects

Intestinal invagination or intussusception is a serious clinical condition resulting from the telescoping of one section of the intestine into itself, as a result of a change in the mobility of the intestine (Figure 8). Attacks of abdominal pain occur every 10 to 15 minutes, together with vomiting and mucousy, bloody stools. A sausage-shaped abdominal mass can also be palpated and, during pain episodes, increased peristaltic noises can be heard.

6.2 Epidemiologic Aspects

Intestinal invagination is rare in infants aged under 3 months and uncommon in infants aged over 36 months. Approximately 80%-90% of all cases generally occur between the ages of 3 and 36 months. The ratio of male to female cases is 3:1.

Figure 8. Intestinal Invagination (Intussusception)



Intussusception is an extremely rare natural phenomenon. The telescoping of the intestine into itself, usually at the ileo-cecal union, leads to a reversible repair or to an entrapment with edema, necrosis, and perforation.
Source: U.S. Centers for Disease Control and Prevention, Atlanta.

6.3 Diagnosis

Intestinal invagination is suspected from the clinical history and physical examination of the patient; the diagnosis is confirmed through radiology (such as barium enema or computerized tomography), ultrasound, or surgery.

6.4 Case Definitions

- **Suspect case**

  Every child aged under 1 year suspected by the physician to have intestinal invagination based on clinical history or physical examination.

- **Confirmed case**

  Every suspect case with diagnosis confirmed by radiology image, ultrasound, or surgical report.

Annex 3 contains a form for reporting and investigating cases of intestinal invagination.

The updated version of this Field Guide can be accessed on the website of the PAHO Immunization Unit:
http://new.paho.org/hq/index.php?option=com_content&task=view&id=278&Itemid=358

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GLOSSARY

Term	Definition
Case-fatality	Expresses as a percentage the number of people diagnosed with a particular disease who die in a given period as a result of it. Term often applied to specific outbreaks of acute disease, in which all the patients are observed further for an appropriate period of time to determine all deaths attributable to the disease.
ESAVI	Event supposedly attributable to vaccination or immunization
Genome	Complete set of genes in the chromosomes of each cell of a given organism
Genotype	Particular genetic constitution of an individual or organism
Heterotypic immunity	Acquired by an individual through high concentrations of antibodies against a serotype or genotype different from the one circulating in his geographical area
Homotypic immunity	Acquired by an individual through high concentrations of antibodies against the virus circulating in his/her geographical area
Immunity	Quality of not being susceptible to or affected by a given disease or process
Morbidity rate	Rate at which a disease affects a particular population in a particular time period
Mortality rate	Incidence of death expressed as a percentage of the total population in a particular population in a particular time period
Neutralizing antibodies	Antibodies that neutralize virus growth on cell linings
Replication	Duplication of DNA polynucleotide chains or synthesis of DNA. In research: exact repetition of an experiment conducted to confirm the initial findings.

Serotype	Determination of antigens expressed by a bacterium or virus.
Strain	Taxonomic subgroup of a species
Viral enterotoxin	Toxic substance specific to the cells of the intestinal mucous membrane

ANNEXES

Annex 1. Rotavirus Diarrhea Reporting and Investigation Form

Annex 2. Data on Rotavirus Diarrhea Surveillance in Sentinel Hospitals

Annex 3. Intestinal Invagination Reporting and Investigation Form

Annex 1. Rotavirus Diarrhea Reporting and Investigation Form

Patient Name: _____

Date of birth: _____/_____/_____ Gender: Male _____ Female _____

Nursing: Exclusively breast-fed _____ Formula _____ Mixed _____ Varied nutrition _____

Name of admitting hospital: _____ Clinical file no: _____

Child enrolled in day-care center? Yes _____ Name of center: _____ No _____

Clinical Data

Date of admission: _____/_____/_____ Date of discharge:_____/_____/_____

Days in hospital to treat diarrhea: _____

Symptoms at time of admission: _____

Fever: Yes _____ No _____ Unknown _____

Vomiting: Yes ____ No. of times in last 24 hours _____ No _____ Unknown _____

Date of onset of diarrhea: _____/_____/_____ No. of episodes in last 24 hours _____

Date diarrhea ended: _____/_____/_____ Unknown _____

Stool characteristics: _____

Watery _____ Semi-liquid _____ Bloody _____ Other _____

Treatment

Antibiotics used prior to hospital admission?

Yes ____ Which? _____ No____ Unknown____

Condition at time of admission: Not dehydrated _____ Dehydrated ____ Dehydrated and in shock ____

Treatment administered on hospital admission: Plan B _____ Plan C _____

Antibiotics received in the hospital: Yes _____ Which? _____ No _____

Complications: _____ No _____ Not known _____

Admitted to intensive care unit? Yes ____ Number of days: _____ No _____

Date of cessation of diarrhea:_____/_____/_____

Reason for release: Improvement _____ Requested _____ Death _____

Laboratory Data

Date sample taken:_____/_____/_____ Unknown_____

No stool sample collected: _____

Date arrived at reference laboratory: _____/_____/_____ Date of results: ____/_____/____

Positive for rotavirus? Yes _____ Serotype G _____ P_____ No _____

Bacteria identified? Yes ____ Which? _____ No____

Parasite identified? Yes ____ Which? _____ No____

Final classification

Confirmed _____ Discarded _____ Inadequate investigation _____

Isolated case _____ Outbreak _____

Person responsible for above information

Name: _____ Telephone: _____

Date investigation began _____/_____/_____

Annex 2. Data on Rotavirus Diarrhea Surveillance in Sentinel Hospitals

Year _____ Hospital _____ Municipality _____

Person in Charge of Information: Name _____ Telephone _____

	January	February	March	April	May	June	July	August	September	October	November	December
1. Number of children < 5 years hospitalized												
2. Number of children < 5 years hospitalized due to diarrhea												
3. Number of children < 5 years meeting criteria of suspect case												
4. Number of suspect cases with adequate stool sample												
5. Number of suspect cases with adequate stool sample and epidemiological form												
6. Number of suspect positive cases with epidemiological form												

Annex 3. Intestinal Invagination Reporting and Investigation Form

Patient Name: _____

Date of birth: _____/_____/_____ Gender: Male ____ Female ____

Admitting hospital: _____ Clinical case no.: _____

Record of rotavirus vaccination

Total number of doses: _____ Date of last dose: _____/_____/_____

Clinical data

Date of hospital admission: _____/_____/_____

Symptoms at time of admission:

Abdominal pain: Yes ___ Date of onset: ____/___/____ No ___ Unknown ___

Fever: Yes ___ Date of onset: ____/___/____ No ___ Unknown ___

Vomiting: Yes ___ Date of onset: ____/___/____ No ___ Unknown ___

Diarrhea: Yes ___ Date of onset: ____/___/____ No ___ Unknown ___

Blood in stool or rectal bleeding? Yes ___ No ___ Unknown ___

Interval between last dose of vaccine and onset of first symptom: _____ days

Diagnosis and treatment

Intestinal invagination by: X-ray ____ Ultrasound ____ Surgery ____

Date intestinal invagination diagnosed: _____/_____/_____

Clinical treatment ____ Surgery ____

Pathology Exam Yes ____ No ____ Unknown ____

Pathology findings: Lymphatic hyperplasia (Peyer's plaque) _____ Intestinal polyps _____

Lymphosarcoma _____ Meckel's diverticulus _____ Other:_____

Complications: Yes ____ What?_____

No ____ Unknown_____

Admitted to intensive care unit? Yes _____ Number of days? _____ No _____

Date: _____/_____/_____

Laboratory data

Stool sample obtained? Yes ____ Date:_____/_____/_____ No ____ Unknown ___

Rotavirus detected? Yes_____ G Serotype: _____ P Serotype and Genotype: _____ No ____

Final Classification

Case onset ____ days after vaccination Yes____ No____

Case associated with rotavirus diarrhea? Yes____ No____

Person responsible for above information

Name: _____ Telephone: _____

Date: _____/_____/_____