

CLINICAL REVIEW

Diagnosis, management, and prevention of rotavirus gastroenteritis in children

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Rotavirus is the leading cause of severe childhood gastroenteritis. Each year, rotavirus is responsible for about 25 million clinic visits, two million hospital admissions, and 180 000–450 000 deaths in children under 5 years of age globally.^{1–3} Although rotavirus infection is prevalent worldwide, most deaths from this infection occur in developing countries (fig 1⇓). Gastroenteritis caused by rotavirus cannot be clinically distinguished from that caused by other enteric pathogens; diagnosis requires testing of fecal specimens with commercially available assays. However, rotavirus is not routinely tested for in patients with gastroenteritis because the results do not alter clinical management, which relies mainly on appropriate rehydration therapy. Orally administered live attenuated vaccines that mimic natural infection offer the best protection against rotavirus. Two licensed rotavirus vaccines have been available since 2006 and have been implemented in many countries. We review approaches to diagnosis, management, and prevention of rotavirus gastroenteritis.

How does rotavirus gastroenteritis present clinically?

The clinical spectrum of rotavirus infection ranges from subclinical illness or mild watery diarrhea of limited duration to frequent profuse diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and death. Rotavirus illness usually begins with acute onset of fever and vomiting, followed one or two days later by frequent watery stools. About 30–40% of children may have a moderate fever (temperature >39°C). Vomiting usually lasts for only one or two days and other gastrointestinal symptoms generally resolve in three to seven days.

Although gastroenteritis is the chief manifestation of rotavirus infection, neurologic features—including benign convulsions (usually afebrile but febrile in some cases), encephalitis or encephalopathy, and cerebellitis—have also been described.⁴ For example, a multicentre study from Canada reported that 7% of 1359 children admitted to hospital with laboratory confirmed rotavirus had seizures at presentation.⁵ A variety of other clinical

conditions (such as sudden infant death syndrome, necrotizing enterocolitis, intussusception, Kawasaki's disease, and type 1 diabetes) have been associated with rotavirus gastroenteritis, but a causal association has not been confirmed. A transient rise in serum transaminase concentrations is also often seen in patients with rotavirus gastroenteritis.

Who gets rotavirus disease?

Rotavirus infects nearly all children in developed and developing countries by 3–5 years of age. Neonatal infections occur but are often asymptomatic or mild, possibly because of protection from maternal antibody. The incidence of clinical illness peaks in children aged 4–23 months, who are also at greatest risk of severe disease that requires hospital admission. Although repeat infections are common (three or more rotavirus infections occurred in about 42% of children by 2 years of age in one follow-up study in a cohort of Mexican children), symptoms are milder with each subsequent infection.^{6,7} Therefore, rotavirus infections are usually subclinical or mild in adults, but they can be severe, particularly in immunocompromised and older people.⁸ Rotavirus is also an important cause of nosocomial diarrhea.

Case-control studies in industrialized countries have shown that lack of breast feeding, prematurity, and low birth weight are associated with increased risk of hospital admission for rotavirus gastroenteritis.^{9,10} Protracted rotavirus diarrhea with prolonged viral excretion and, in rare instances, systemic dissemination has been described in severely immunodeficient children, particularly those with severe T cell and combined T and B cell deficiencies. People who are immunosuppressed in preparation for bone marrow transplantation are also at risk for severe or even fatal rotavirus disease.

In all regions of the world, rotavirus is the leading cause of hospital admission for gastroenteritis. A systematic review of 131 surveillance studies published from 2001 to 2011 found that rotavirus accounted for 33–49% of hospital admissions for gastroenteritis in countries in different geographic regions and

Summary points

- Rotavirus is the leading cause of severe gastroenteritis in children worldwide, accounting for 35-40% of hospital admissions for gastroenteritis
- Each year, 180 000-450 000 children under 5 years die from rotavirus gastroenteritis, with more than 90% of deaths occurring in developing countries
- Because nearly all children are affected by rotavirus by age 5 years, good sanitation and hygiene alone are inadequate for prevention
- Orally administered live attenuated vaccines offer the best protection against rotavirus; as of December 2013, national immunization programs of 51 countries include rotavirus vaccine
- Such programs have greatly reduced morbidity and mortality from gastroenteritis
- A low risk of intussusception has also been documented post-licensure in some countries, but this risk is greatly exceeded by the health benefits of vaccination

Sources and selection criteria

We looked at recent conference proceedings and searched PubMed, the Cochrane Database of Systematic Reviews, and Clinical Evidence online using the terms "rotavirus", "rotavirus gastroenteritis", and "rotavirus vaccines". We focused on systematic reviews, meta-analyses, and high quality randomized controlled trials published in English within the past 10 years (2004-13).

with varying levels of child mortality.² However, more than 90% of global deaths from rotavirus occur in low income countries in sub-Saharan Africa and South Asia, mainly because of suboptimal access to healthcare, including basic hydration therapy. In addition, compared with industrialized countries, severe rotavirus gastroenteritis occurs at a younger age in developing countries (up to two thirds of all paediatric disease occurs in the first year of life) and coinfections with other enteric pathogens are more common.

In temperate climates, rotavirus gastroenteritis shows prominent seasonality, occurring mainly during the fall and winter, with little disease activity during summer months.¹¹ In tropical countries, rotavirus occurs all year round, although incidence often increases during the cool dry months.

How do rotaviruses cause diarrhea?

Mechanisms of rotavirus pathogenesis have been studied in animal models and humans. The infectious dose of rotavirus is estimated to be 100-1000 viral particles.¹² Transmission of rotavirus occurs mainly through the fecal-oral route, and viral spread can occur through contaminated hands, environmental surfaces and objects, and occasionally food and water. Rotavirus exclusively infects the mature differentiated enterocytes found at the tips of the villi in the small intestine (fig 2↓). Attachment of rotavirus to its sialoglycoprotein and integrin receptors is mediated mainly by viral protein 4 (VP4), but neutralizing antibodies directed against VP4 or VP7 (or both) can prevent viral binding and penetration. Infection of the enterocyte leads to virus entry, uncoating of the virus, transcription of nucleic acid, translation of viral proteins, formation of viroplasm, and apical release of the virus and viral protein by a non-classic secretory pathway.¹³ The progeny virus are produced after 10-12 hours and released in large numbers into the intestinal lumen. Rotavirus can infect neighboring cells, leading to continued replication and shedding, which consists initially of a high viral load. In children, the viral load decreases rapidly as diarrhea resolves, but viral nucleic acid can be detected at low levels for several weeks.¹⁴

The pathogenesis of rotavirus diarrhea includes effects on absorption and on secretion. Morphologically, rotavirus infection causes enterocyte death and desquamation, leading to the loss of absorptive villous cells and the proliferation of secretory crypt cells.¹⁵ Malabsorption may also result from a virus induced reduction in the expression of absorptive enzymes, as well as paracellular leakage as a consequence of functional changes in

tight junctions between enterocytes, which may be mediated by the viral non-structural protein 4 (NSP4). Biopsies show atrophy of the villi and mononuclear cell infiltrates in the lamina propria. Increased chloride secretion and loss of consequent water and electrolyte are mediated by NSP4, which acts as a viral enterotoxin, activating cellular calcium channels and inducing secretory diarrhea. Activation of the enteric nervous system (also thought to be dependent on NSP4) induces secretory diarrhea and increases intestinal motility.¹³ Villous brush border enzymes such as sucrase and isomaltase also decrease, resulting in accumulation of undigested sugars in the intestinal lumen. This increases the osmotic gradient, which in turn favours further fluid secretion.

Rotavirus infection was previously thought to be limited to the intestine, but several studies over the past decade have shown that rotavirus causes short term viremia in immunocompetent infants as well as in experimentally infected animals.¹⁶ The clinical relevance of this systemic spread of rotavirus remains unclear, but it may be linked to the extraintestinal clinical manifestations associated with rotavirus infection.

How is rotavirus diagnosed?

Rotavirus can be detected in stool specimens from children with gastroenteritis by several techniques, including electron microscopy, polyacrylamide gel electrophoresis, antigen detection assays, reverse transcription polymerase chain reaction (RT-PCR), and virus isolation. Diagnosis of rotavirus was initially by electron microscopy, with and without agglutination by immune sera. Large numbers of rotavirus particles (up to 10¹¹/g feces) are excreted during the acute phase of infection, and children with severe diarrhea seem to excrete a greater number of viruses.¹⁷ Polyacrylamide gel electrophoresis detects rotavirus RNA extracted directly from stool specimens; the electrophoretic migration pattern of the 11 segments of the double stranded RNA genome permits analysis of the relatedness of circulating strains.¹⁸

Children with gastroenteritis are not routinely tested for rotavirus because the results do not alter treatment. When testing is performed, antigen detection tests—including commercially available enzyme linked immunosorbent assays (ELISAs) and immunochromatographic assays—are widely used. Most of these tests have high sensitivity and specificity (90-95%).¹⁹ RT-PCR is widely used in research laboratories to detect the viral genome.²⁰ It provides data on the VP7 and VP4 genotypes

that form the basis of binary classification (G and P type, respectively) of rotavirus strains.

How is rotavirus gastroenteritis treated?

The management of acute rotavirus gastroenteritis focuses on the treatment and prevention of dehydration. In most situations the clinician will not be aware at the start of treatment whether the gastroenteritis is caused by rotavirus or another pathogen. Initial assessment therefore focuses on determining the degree of dehydration because this will be used to guide and monitor treatment.

Many evidence based reviews and clinical guidelines are available on various aspects of the assessment and treatment of acute gastroenteritis in young children.²¹⁻³⁶ However, a recent systematic review of eight guidelines noted considerable variation in their quality, inconsistencies between the recommendations, lack of evidence for many recommendations, and lack of generalisability to general practice.³⁷ These were suggested as possible reasons why adherence to such guidelines is poor in high income countries. For example, the authors noted that in general practice it was unclear “how” or to “whom” oral rehydration therapy should be given. They concluded that future studies, particularly in general practice, need to determine the value of clinical signs and symptoms in assessing dehydration, the optimal dose of oral rehydration solution for each grade of dehydration, and the validity of reasons why clinicians prescribe other drugs. In contrast, another recent assessment of the quality of clinical practice guidelines for acute gastroenteritis, using the appraisal of guidelines for research and evaluation instrument, concluded that the overall quality of these guidelines was fair.³⁸

How should dehydration be assessed?

Several scoring systems have been devised to assess dehydration.³⁹ The World Health Organization scale is probably most widely used in the developing world (table 1),⁴⁰ whereas the modified four point Gorelick score (box) and clinical dehydration scale (table 2) have been used in developed world settings.^{32-34 39} The clinical dehydration scale has been reported to help predict a longer length of stay and the need for intravenous fluid rehydration.³² It is generally accepted that conventional clinical signs of dehydration are valid and reliable when used collectively but individually they lack sensitivity and specificity.⁴¹ The Vesikari and Clark scores are used in rotavirus vaccine efficacy trials for assessing the severity of gastroenteritis but are not designed to guide clinical management according to the degree of dehydration.³⁵

Oral and intravenous rehydration therapy

Oral and intravenous rehydration is the mainstay of treatment for rotavirus and other causes of acute gastroenteritis. Oral rehydration therapy is the preferred treatment of mild to moderate dehydration in children with acute diarrhea.^{27 29 41} For every 25 children (95% confidence interval 14 to 100) treated one will not respond and will require intravenous rehydration.²⁷ Expert consensus recommends that children who are very ill, lethargic, drinking poorly, or have shock or near shock are initially treated intravenously. Oral rehydration therapy should not be given to children with intestinal ileus until bowel sounds are audible, or in the presence of glucose malabsorption.²⁹

For more than two decades, WHO recommended the standard glucose based oral rehydration solution (90 mmol/L sodium, 111 mmol/L glucose, and a total osmolarity 311 mmol/L).²⁸

However, subsequent studies have shown that when compared with the standard WHO solution, reduced osmolarity oral rehydration solution is associated with fewer unscheduled intravenous fluid infusions (odds ratio 0.59, 0.45 to 0.79), lower stool volume after randomization, less vomiting, and no increased risk of hyponatremia.²⁸ In 2002, WHO recommended the routine use of a solution with reduced osmolarity (sodium 75 mmol/L, glucose 75 mmol/L, and total osmolarity 224 mmol/L) for non-cholera diarrhea.

To maintain hydration of children with “no signs of dehydration,” WHO recommends giving extra fluid or oral rehydration solution after each loose stool. The suggested volume is 50-100 mL (quarter to half a large cup) for children under 2 years of age and a 100-200 mL (half to one large cup) for those above 2.⁴⁰ For children with “some signs of dehydration,” WHO recommends correcting hydration over four hours with 75 mL/kg of solution.⁴⁰ However, a review of eight international guidelines showed that recommendations on the dose of oral rehydration solution were not evidence based and were inconsistent, reflecting the use of expert opinion and differences in how guidelines categorized dehydration.³⁷ The authors concluded that the optimal regimen was unclear.

It is important that breast feeding should continue throughout the rehydration and maintenance phases of treatment.⁴⁰ Feeding should be restarted as soon as possible because this will reduce the duration and severity of diarrhea, and there is no evidence that early refeeding increases the risk of unscheduled intravenous fluid use, episodes of vomiting, or development of persistent diarrhea.²² Although lactose-free feeds may reduce the duration of diarrhea in children with mild to severe dehydration compared with feeds containing lactose, there is no evidence that lactose containing feeds are harmful for most children with acute gastroenteritis.⁴²

Randomized controlled trials—including some that specifically assessed efficacy against rotavirus gastroenteritis—have shown that other treatments such as probiotics, zinc, ondansetron, nitazoxanide, and some biological compounds are effective in the management of acute gastroenteritis.^{21 23 24 40-45} However, recommendations for the use of these treatments vary considerably between different developmental regions and different countries, and further discussion of their use is beyond the scope of this article.

How can rotavirus gastroenteritis be prevented?

Because rotavirus infects nearly all children in both industrialised and developing countries early in life, good hygiene and sanitation alone are considered inadequate for prevention. Observational studies have shown that breast feeding confers protection from rotavirus gastroenteritis, although one case-control study indicated that it may only postpone the occurrence of rotavirus gastroenteritis to the post-weaning period.⁴⁶

Follow-up of birth cohorts indicates that, although children can be infected with rotavirus four to five times in the first two years of life, the incidence of severe rotavirus gastroenteritis is reduced with each repeat infection.^{6 7} Therefore, orally administered, live, attenuated rotavirus vaccines have been developed to mimic the effect of natural infection and prevent severe rotavirus disease.

A rhesus-human reassortant rotavirus vaccine (Rotashield, Wyeth) was licensed in the US in 1998 after showing high efficacy against severe rotavirus gastroenteritis in randomized

Four point modified Gorelick score^{33 34}

1 point for each of the signs listed below:

- Ill general appearance
- Absent tears
- Dry mucous membranes
- Capillary refill >2 s

≤1 points: maintain hydration (<5% dehydration).

2 points: needs oral rehydration (5-10% dehydration).

3-4 points with normal vital signs: needs intravenous rehydration (>10% dehydration).

Abnormal vital signs (increased heart rate, decreased blood pressure, decreased level of consciousness, increased capillary refill time): needs resuscitation.

clinical trials.⁴⁷ Rotashield was recommended for routine immunization of US infants the same year but was abruptly withdrawn a year later because post-licensure observational studies found that it was associated with a severe adverse event, intussusception.^{48 49} Intussusception is a form of bowel obstruction that often requires surgery and is associated with high fatality if not treated. It was estimated that vaccination of 10 000 infants with Rotashield resulted in one excess case of intussusception.

Two other live oral rotavirus vaccines—a pentavalent bovine-human reassortant vaccine (RotaTeq, Merck) and a monovalent human vaccine (Rotarix, GSK Biologicals)—were in advanced stages of clinical testing when Rotashield was withdrawn (table 3). RotaTeq and Rotarix were each tested in randomized clinical trials of 60 000-70 000 infants to assess the risk of intussusception before licensure.^{50 51} No increase in risk was found during the 42 and 30 days post-vaccination after the three doses of RotaTeq or two doses of Rotarix, respectively. The vaccines showed 85-98% efficacy against severe rotavirus gastroenteritis in these trials conducted in the Americas and Europe, with good protection against disease caused by rotavirus strains not included in the vaccines (heterotypic immunity). These findings supported vaccine licensure and recommendations for use by policy groups in the US and Europe and by WHO.⁵²

As of December 2013, 51 countries include rotavirus vaccines in their national immunization programs. A systematic review of ecologic studies from eight countries reported a 49-89% decline in laboratory confirmed rotavirus hospital admissions and 17-55% reduction in all cause hospital admissions for gastroenteritis in children under 5 years within two years of vaccine introduction.⁵³ Unexpectedly, rotavirus vaccination of young infants has also resulted in decreases in rotavirus disease in children who missed vaccination, older children, and even adults who were not eligible for vaccination.⁵⁴ This phenomenon, known as herd protection, is probably related to reduced transmission of rotavirus in the community as a result of vaccination. Reductions in nosocomial rotavirus infections have also been seen since the introduction of the vaccine.⁵⁵ Lastly, ecologic studies from Mexico and Brazil have shown a 35% and 22% decline in childhood deaths from diarrhea, respectively, since the introduction of the vaccine,^{56 57} and these reductions have been sustained for four years in Mexico. These findings are particularly noteworthy because vaccine efficacy against death from diarrhea was not evaluated in pre-licensure trials.

Post-licensure observational studies in several countries, including the US, Australia, Mexico, and Brazil, have also identified a low risk of intussusception with both rotavirus vaccines.⁵⁸⁻⁶⁵ The evidence of risk for the two vaccines is difficult to compare directly because the study populations and designs differed. In general, the overall risk is one to five excess cases of intussusception per 100 000 vaccinated infants. Considering

the substantial and well documented health benefits of vaccination against this low intussusception risk, policy makers in countries with documented risk, as well as global health authorities such as WHO, strongly support rotavirus vaccination of infants.

Live oral vaccines against many diseases, such as polio, typhoid, and cholera, have performed less well in developing countries than in industrialised ones. The reasons for this variability are not completely understood. Potential explanations include interference in vaccine uptake by greater levels of maternal antibody or concurrent enteric infections in developing countries, as well as reduced immune response in infants because of comorbidities or malnutrition, including micronutrient deficiencies.⁶⁶

Because of these concerns, randomised efficacy trials of both RotaTeq and Rotarix were conducted in developing countries in Africa and Asia.⁶⁷⁻⁶⁹ These trials showed modest vaccine efficacy (50-64%) against severe rotavirus gastroenteritis. Despite this reduced efficacy, the public health benefits of vaccination in terms of number of severe rotavirus gastroenteritis episodes prevented per 100 infants was greater in developing than in industrialised countries. This is because of the substantially greater rate of severe rotavirus gastroenteritis in developing countries. These considerations led WHO to issue a global recommendation for vaccination in 2009 and have prompted several low income countries to include rotavirus vaccination in their immunization programs.

As rotavirus vaccines are introduced into immunization programs of low income countries globally, it will be important to assess the real world impact of vaccination to gain a better understanding of vaccine effectiveness and safety in a range of settings. Although both of the licensed rotavirus vaccines have shown good protection against a range of circulating rotavirus strains, including strains with either or both G and P types not contained in the vaccine, further monitoring of the long term impact of vaccination on strain ecology is vital. Also, given the moderate efficacy of rotavirus vaccines in low income countries, interventions to improve vaccine performance (such as additional vaccine doses or different vaccination schedules) should be considered and evaluated. Finally, to sustain global implementation of vaccination, an adequate supply of affordable rotavirus vaccines must be assured. It is therefore encouraging that several manufacturers in emerging markets, including India, China, Indonesia, and Brazil, are developing candidate rotavirus vaccines that may be available within the next five years.

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Areas for future research

- Exploring the role of rotavirus in extraintestinal clinical syndromes (such as neurologic manifestations, necrotizing enterocolitis)
- Investigating the value of clinical signs and symptoms in assessing dehydration, particularly in general practice
- Defining the optimal dose of oral rehydration solution for each grade of dehydration, so that consistent recommendations can be made
- Identifying treatments (including antiviral agents) with clinical efficacy against rotavirus gastroenteritis
- Community based action research and sociocultural research on knowledge, attitudes, perceptions, cultural practices, and health seeking behaviours with regard to rotavirus infection
- Understanding the benefit-risk profile of routine rotavirus vaccination in a diverse range of geographic and socioeconomic settings
- Investigating the effectiveness and impact of rotavirus vaccination in low income settings
- Identifying interventions (such as additional vaccine doses or alternate schedules, supplementation with micronutrients) or alternative approaches (such as parenteral vaccines) that might improve the performance of rotavirus vaccines in low income settings

Additional educational resources

Resources for healthcare professionals

- Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2009;58(RR02):1-25. www.cdc.gov/mmwr/preview/mmwrhtml/rr5802a1.htm (free access)
- WHO. WHO position paper on rotavirus vaccines. *Wkly Epidemiol Rec* 2013;88:49-64. www.who.int/wer/2013/wer8805.pdf (free access)
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- PATH (<http://sites.path.org/rotavirusvaccine/rotavirus-advocacy-and-communications-toolkit/>)—Free rotavirus disease and vaccine resources
- PATH (<http://sites.path.org/rotavirusvaccine/current-issue-of-rotafash-jpg/>)—Breaking news and updates on rotavirus vaccines

Resources for patients and parents

- Centers for Disease Control and Prevention at (www.cdc.gov/rotavirus/index.html)—Basic information on the symptoms, treatment, and prevention of rotavirus gastroenteritis

Tips for non-specialists

- All children are infected with rotavirus in the first 3-5 years of life, regardless of hygiene and sanitation conditions
- Vaccines are therefore the most effective way to prevent rotavirus diarrhea
- Treatment of rotavirus diarrhea relies on hydration therapy
- Rotavirus vaccines have performed well in countries where they are used routinely; in some settings, they have conferred additional benefits to unvaccinated children and adults through herd protection
- Although rotavirus vaccines work less well in developing countries, the potential to prevent severe disease and deaths is greater because of the high disease burden in these settings
- The documented health benefits of rotavirus vaccines far outweigh the small risk of intussusception that has been seen in some settings

UDP and GK—none. EASN has participated in vaccine and disease surveillance studies funded by GlaxoSmithKline and Pfizer.

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Tables

Table 1 | World Health Organization guidelines for assessing dehydration in children with acute gastroenteritis⁴⁰

	A	B	C
Condition*			
Well, alert		Restless, irritable	Lethargic or unconscious
Eyes†			
Normal		Sunken	Sunken
Thirst			
Drinks normally, not thirsty		Thirsty, drinks eagerly	Drinks poorly, or not able to drink
Skin pinch‡			
Skin goes back quickly		Skin goes back slowly	Skin goes back very slowly
Decision			
No signs of dehydration		Some dehydration if there are ≥ 2 signs in B	Severe dehydration if there are ≥ 2 signs in C

*Being lethargic and sleepy are not the same. A lethargic child is not simply asleep: the child's mental state is dull and the child cannot be fully awakened; the child may appear to be drifting into unconsciousness.

†In some infants and children the eyes normally appear somewhat sunken. It is helpful to ask the mother if the child's eyes are normal or more sunken than usual.

‡The skin pinch is less useful in infants or children with marasmus or kwashiorkor, and in obese children.

Table 2| Clinical dehydration scale³²

Characteristic	Score*		
	0	1	2
General appearance	Normal	Thirsty, restless, or sleepy; irritable when touched	Drowsy, limp, and cold; may be comatose
Eyes	Normal	Slightly sunken	Deeply sunken
Tongue	Moist	Sticky	Dry
Tears	Present	Decreased	Absent

*Total score: 0=no dehydration; 1-4=some dehydration; 5-8=moderate/severe dehydration.

Table 3| Features of Rotarix and RotaTeq rotavirus vaccines

Feature	Rotarix	RotaTeq
Composition	Single human rotavirus strain (P1A[8], G1)	Five human G/P reassortants with bovine rotavirus strain WC3 (P7[5], G6): G1 × WC3; G2 × WC3; G3 × WC3; G3 × WC3; P1A[8] × WC3
Number of doses needed	2 oral doses	3 oral doses
Schedule*	Dose 1: minimum 6 weeks of age; dose 2: ≥4 weeks later; complete by 24 weeks of age	Dose 1: 6-12 weeks of age; doses 2 and 3: 4-10 week intervals; complete by 32 weeks of age
Dose	Each dose (1-1.5 mL) contains at least 10 ⁶ median cell culture infectious doses	Each dose (2 mL) contains at least 2.0-2.8×10 ⁶ infectious units per reassortant
Shelf life	36 months	24 months
Storage	2-8°C, protected from light	2-8°C, protected from light
Contraindications	History of hypersensitivity to the vaccine or any component of the vaccine; history of uncorrected congenital malformation of the gastrointestinal tract that would predispose to intussusception; history of severe combined immunodeficiency disease; history of intussusception	History of hypersensitivity to the vaccine or any component of the vaccine; history of severe combined immunodeficiency disease; history of intussusception

*Ages for vaccine doses vary according to the recommendations of individual countries and vaccination schedules.

Figures



Fig 1 World Health Organization estimates of rotavirus mortality (deaths/100 000 children under 5 years of age) by country in 2008. Reproduced, with permission, from *Lancet Infectious Diseases*²

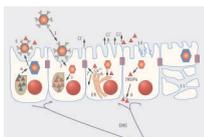


Fig 2 Mechanisms of rotavirus pathogenesis. Most information on rotavirus pathogenesis is derived from small animal models. Infection leads to attachment of the rotavirus to enterocytes (1), uncoating of the virus (2), followed by transcription and translation of viral proteins (3). This leads to the formation of a viroplasm, from which double layered particles assemble (4) and acquire outer coat proteins to form triple layered mature particles, which are shed by a non-classical secretory pathway (5). The viral enterotoxin non-structural protein 4 (NSP4; red triangles) is also released with the mature virions. NSP4 induces the release of intracellular calcium (Ca^{2+}) (6) from the endoplasmic reticulum (ER) and disrupts tight junctions (7), resulting in paracellular leakage of fluid and electrolytes. NSP4 can act on crypt cells to induce chloride (Cl^-) secretion directly (8) or through the enteric nervous system (ENS) (9), both of which draw water into the lumen. A decrease in brush border enzymes induced by infection (10) results in accumulation of sugars in the lumen and osmotic fluid loss. Destruction of intestinal cells later in infection results in loss of surface area and a malabsorptive diarrhea (11)