Rotavirus Infection in Neonates and Young Infants

Preeti Shakya¹, Biplov Adhikari², Amit S Nepal³, Pragyik Pandey⁴, Akhil Maheshwari⁵

ABSTRACT
Rotavirus is the primary cause of acute, frequently severe gastroenteritis among growing premature neonates, young infants, and children under the age of five globally. It contains a double-stranded ribonucleic acid genome is a member of the Reoviridae family. In this review, we have discussed the structure and characteristics of the virus, the pathogenesis of rotaviral diarrhea, clinical features, methods of diagnosis, clinical management, and available vaccines. This article combines peer-reviewed evidence from our own clinical studies with results of an extensive literature search in the databases PubMed, EMBASE, and Scopus.

Keywords: Diarrhea, Double-stranded ribonucleic acid, Gastroenteritis, Nonenveloped virus, Reovirus, Vaccine, World Health Organization.

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INTRODUCTION
Rotaviruses are one of the leading causes of life-threatening acute gastroenteritis among infants and young children worldwide. It is associated with substantial morbidity and mortality, mostly in developing countries. World Health Organization estimates that about 453,000 children aged under 5 years die each year from rotavirus infections worldwide. The infections begin occurring during the neonatal period, and the number increases significantly beyond 3 months of age. This article reviews the rotavirus disease burden, its pathogenesis, clinical presentation, management, complication, and the latest developments in its treatment including vaccination.

Virology
Rotaviruses are members of the rotavirus genus of the Reoviridae family. Rotaviruses are large particles (1000 Å) comprised of a viral genome surrounded by three concentric protein layers. In electronic micrographs, rotaviruses appear “wheel-shaped” with a central axle composed of a few dots and concentric linear shadows in the periphery. The genome is composed of 11 segments of double-stranded ribonucleic acid (dsRNA) that encodes six viral proteins (VPs) and six nonstructural proteins (NSPs). Two of the VPs, VP1, and VP3 have an enzymatic role, whereas VP2, VP4, VP6, and VP7 contribute to the structure (Fig. 1). Each genome segment codes for one protein with the exception of segment 11, which codes for two proteins. The role of these proteins is summarized in Table 1.

Rotavirus species are classified on the basis of antigenic differences of VP6 and genetic sequence. Ten different species (A-J) have been identified. Serogroups A, B, and C are most commonly implicated in humans. Group A rotaviruses are the single most common serogroup of human rotaviruses.

Rotaviruses exhibit unusual structural and replication properties that allow them to establish clinically significant disease. The capsid, comprising three layers, is extremely stable and ensures feco-oral transmission as well as delivery of viral particles to the intestine. The capsid contains 60 spikes that project from its surface which are the initial viral attachment proteins—these complex molecules bind to the receptors on the enterocytes. These spikes undergo conformational change following proteolytic cleavage by trypsin. The virus, which does not get fully uncoated, gets its outer capsid removed to deliver the dsRNAs that then produce capped messenger RNAs (mRNAs) which are then translated into proteins and new genomic RNA. The molecular mechanisms involved in rotaviral disease are shown in Figure 2.

The rotavirus NSPs are produced in infected cells and help in viral replication. These NSPs act on the host cells and play a major role in the pathogenesis of rotaviral disease. The VP7, a glycoprotein (G-type antigen), forms the outer capsid shell, and the VP4, which forms spikes that protrude through the protein capsid shell, form the basis for the classification system (binary) of viral serotypes. The VP7 protein is an important neutralization target (Table 1). Based on genotype sequencing and neutralization assays, severe serotypes of VP7 have been recognized and classified as the G serotypes (named as the G1, G2, G3, and so on). On the other hand, VP4 serotypes are not so consistent in neutralization assays and genotyping sequencing. These proteins have been classified using a dual system, including a (a) P subtyping, where P genotypes are denoted using numerals in brackets (such as P[8], P[4], and so forth); and (b) P serotypes, which are classified in a numerical order (such as P1, P2, and so on). Currently, 32 G and 48[P] subtypes are known. Fortunately, both sets of proteins are recognized by the host immune system; these induce antibody responses and therefore can be used to augment the host’s defense responses.

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The virion core is composed of dsRNA and the VP1/VP3 that have an enzymatic role, and these are enclosed in the inner capsid composed of VP2. The core is covered by a middle capsid layer of VP6, and an outer capsid of VP7. The outer layer has spikes composed of VP4, which can be proteolyzed into VP5 and VP8. VP6 in the middle capsid layer determines species, group, and subgroup specificities. VP4 and VP7 in the outer capsid are antigenic and elicit immune responses with specific antibodies.

### Table 1: Rotavirus viral proteins (VPs) and non-structural proteins (NSPs)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP1</td>
<td>Polymerase</td>
</tr>
<tr>
<td>VP2</td>
<td>Inner capsid (protein shell)</td>
</tr>
<tr>
<td>VP3</td>
<td>Capping enzyme</td>
</tr>
<tr>
<td>VP4</td>
<td>Neutralization target; breaks into VP5 and VP8</td>
</tr>
<tr>
<td>VP6</td>
<td>Middle shell</td>
</tr>
<tr>
<td>VP7</td>
<td>Neutralization target</td>
</tr>
<tr>
<td>NSP1</td>
<td>Interferon antagonist</td>
</tr>
<tr>
<td>NSP2</td>
<td>Octamers regulate viroplasm formation and, possibly, function in reassortment restriction between rotavirus groups</td>
</tr>
<tr>
<td>NSP3</td>
<td>Promotes systemic spread; promotes viral mRNA translation by directing circularization of viral polysomes. In addition, may inhibit translation of and relocalization of host polyadenylated mRNAs from cytoplasm to nucleus</td>
</tr>
<tr>
<td>NSP4</td>
<td>Enterotoxin; mobilizes intracellular calcium in human intestinal cells by stimulating phospholipase C-mediated inositol 1,4,5-trisphosphate production</td>
</tr>
<tr>
<td>NSP5 and NSP6</td>
<td>Viroplasm</td>
</tr>
</tbody>
</table>

Fig. 1: Rotavirus. (A) Electron microscopy shows rotaviruses as spherical particles with short spikes; (B) Schematic diagram of the virus particle. In (A), the virion core is composed of dsRNA and the VP1/VP3 that have an enzymatic role, and these are enclosed in the inner capsid composed of VP2. The core is covered by a middle capsid layer of VP6, and an outer capsid of VP7. The outer layer has spikes composed of VP4, which can be proteolyzed into VP5 and VP8. VP6 in the middle capsid layer determines species, group, and subgroup specificities. VP4 and VP7 in the outer capsid are antigenic and elicit immune responses with specific antibodies.

Fig. 2: Intracellular replication of rotaviruses
Epidemiology

Occurrence

Human rotaviruses were discovered 52 years ago, as an important cause of diarrhea in infants and children across the world. These viruses are one of the most common causes of diarrhea in children younger than 5 years of age, particularly in children between the age of 6 months and 2 years. The incidence of primary rotavirus infection may vary between low- and high-income countries; in developing countries, the rotavirus infections occur frequently in infants, and 80% of all children get infected during the first year after birth. Some studies show the median age of acquisition of rotavirus infections to be between 6 and 9 months, whereas others show the infections to start much earlier. In the developed world, the infections may start later during infancy and may affect young children at 2–5 years of age.

Rotavirus infections have been documented in neonates, particularly in the developing world. Newborn nurseries in many parts of the world have reported outbreaks of rotavirus diarrhea. These epidemics can last for extended periods; an outbreak lasted for over 2 years in Sweden. Newborn infants can develop rotavirus diarrhea soon after birth and can begin shedding the virus in feces starting as early as the first week following birth (both above). Studies have found that 3.5–15% neonates in hospital nurseries excrete rotavirus in the feces, and this prevalence can reach up to 50% during outbreaks. Up to 28% of neonates excreting rotavirus particles exhibited diarrhea and other clinical symptoms.

During the early 1980s, rotaviruses were implicated in 870,000 deaths per year in children below the age of 5 years. Nearly one in five children may visit a clinic for rotavirus diarrhea by the age of 5 years. One in 50 children may be hospitalized, and 1 in 205 may die. In 2013, 215,000 children below 5 years of age succumbed to rotavirus gastroenteritis. It has been estimated that each year rotavirus is responsible for 114 million diarrheal episodes, 24 million hospital visits and 2.4 million hospitalizations.

Rotavirus infections are more severe and rampant in low- and middle-income countries. More than 85% of these deaths occurring in low-income countries of Africa and Asia factors like malnutrition, frequent concurrent infections, overcrowding, and poor living conditions including lack of clean water, proper sanitation and unhygienic practices perpetuate and make children living in such reasons more vulnerable to the disease. Almost half of all rotavirus deaths were estimated to occur in Nigeria, India, and Democratic Republic of Congo (DRC); almost three-fourth (73%) of all global mortality occurred in 10 countries.

Reservoir

The gastrointestinal tract and stool of infected humans act as the reservoir of rotaviruses. Even though rotavirus infection occurs in many mammals other than humans, transmission from animals to humans is found to be uncommon. Human infections have not been reported from animal strains. A true carrier state has not been identified, but immunocompromised people may shed the virus for a prolonged period.

Transmission and Communicability

Rotavirus is highly contagious and is considered to be a universal infection. Nearly all children aged 3–5 years were exposed to the infection prior to the pre-vaccine era. The virus is shed in high concentrations in the stool of infected infants beginning 2 days before the onset of diarrhea and for several days after the onset of symptoms. In immunodeficient patients, rotavirus may be detected in stool for more than 30 days after infection.

At room temperature, the viral particles can survive for months in stool samples. Transmission is primarily by the fecal–oral route and can occur via both person-to-person contact or by fomites. It is common for the virus to spread within families, institutions, hospitals, and child care settings.

Seasonal Variation

In temperate climates, rotaviral epidemics usually occur during the fall and winter. The seasonal variations are less distinct in tropical climates although the transmission may be more common during the relatively drier and cooler months. A biennial pattern of disease activity has been noticed with less notable differences in timing by geographic region post vaccine introduction.

Pathophysiology

Rotavirus diarrhea has different mechanisms, including malabsorption secondary to enterocyte destruction, virus-encoded toxin, stimulation of enteric nervous system (ENS), and villus ischemia. Rotavirus accesses the intestines through the mouth and replicates in mature, nondividing enterocytes in the middle and the tip (upper two-third) of villi and enteroendocrine cells in the small intestine.

Rotavirus attaches to host cells by outer capsid protein VP4 via its VP8 domain, binding partners on the host cell surface, include siglogycans like gangliosides GM1 and GD1a and HBGAs (histo-blood group antigens). The virus then starts replicating in the upper small intestine, leading to the destruction of absorptive enterocytes and thus decreases surface area leading to malabsorption. Rotavirus stimulates intestinal secretion via the NSP4 and activation of the enteric nervous system. Osmotically active infectious particles are also released into the intestinal lumen. These osmotically active infectious particles impair water reabsorption in the large intestine, thus causing watery diarrhea.

Along with enterocyte destruction, absorption of sodium, water, and mucosal disaccharides are decreased but mucosal cyclic AMP is unaltered. Malabsorption results in the transit of undigested mono- and disaccharides, carbohydrates, fats, and protein into the colon, further perpetuating osmotic diarrhea. Studies also show epithelial damage caused by villus ischemia can cause diarrhea. The pathogenesis of rotaviral diarrhea is still an area for intense study (Flowchart 1).

Animal studies have shown no visible lesions or slight lesions like enterocyte vacuolization/loss, or larger changes like villus blunting and crypt hyperplasia, suggesting that there is no absolute correlation between histological lesions and disease symptoms.

Clinical Features

The incubation period of rotavirus is usually short and varies between 1 and 3 days. Infections may be asymptomatic—43–78% of rotavirus infections in neonates may be asymptomatic. Although clinically silent, studies show that natural infections in neonates may confer protection against severe disease in the future.

The most common presenting features are fever, diarrhea, and vomiting. Vomiting is usually the first to occur, followed by mild watery diarrhea of short duration to severe diarrhea with vomiting and fever. Fever is found in approximately 33% of infected patients.

In one study done in Korea, the clinical symptoms among premature and full-term babies were found to vary. Premature
neonates manifested lethargy, feeding difficulties, and abdominal
distension, whereas those born at full-term babies were more likely
to have fever, diarrhea, and vomiting. 24

The clinical manifestations of rotaviral infections vary and
depend on whether it is the first infection or reinfection. The
symptoms are more severe in patients if the first infection is after
3 months of age. Younger infants usually present with relatively
less intense symptoms. In few cases, infants have presented with
necrotizing enterocolitis. 21

The symptoms of rotavirus infection are usually identical
with other acute gastrointestinal infections, but these tend to
be more severe in presentation. In addition, it is also difficult
to differentiate rotavirus infection from other pathogens causing
gastrointestinal infections with only the physical examination.
Some common physical examination findings include fever, and
signs of dehydration such as dry mucous membranes, decreased
skin turgor, tachycardia, diminished urine output, and prolonged
capillary refill. 25 Most cases take 5–7 days for recovery.

**Effect of Age on Clinical Severity of Rotaviral Disease**

Age is an important determinant of disease severity. There is some
variability in the severity of rotaviral disease in young infants.
With low antibody levels, premature neonates can develop severe
disease during the first month and during early infancy. Many
young infants born at full term can also develop severe symptoms,
but clear predictive factors are not clearly known. 26 Many full-term
infants can tolerate the infection with minimal symptoms because
of protective levels of the antibodies received from their mother
during the third trimester. However, these infants could become
reservoirs of disease. Neonates can also become symptomatic with
infections with unusual viral strains that are not frequently seen in
the community. During follow-up, many full-term infants can again
become susceptible to rotaviral disease at the age of 6 months
to 2 years, when immunity from passively-received maternal
antibodies begins to wane.

Studies conducted in temperate as well as tropical regions show
formation of anti-rotaviral antibodies in children only by the age of
3 years. 27 In infants who recover from rotaviral infections, develop
IgA, IgG, and neutralizing antibodies that may protect them against
subsequent infections. 28 Various studies have shown a significant
correlation between the formation of neutralizing antibodies, both
in the bloodstream (IgA, IgG) and in stool (IgA), and the protection
from severe disease.

**Investigation**

In most cases, rotavirus infections manifest with a mild fever
accompanied by vomiting and watery diarrhea. Fortunately,
intestinal hemorrhage occurs in a smaller subset. The detection
of acid-reducing substances in the stool, and reduced serum
bicarbonate levels are also more likely to be found in rotavirus
induced gastroenteritis. 4 Currently, lab testing offers the only way
to confirm the diagnosis, and can assist in designing appropriate
treatment and shortening the hospital stay. 29

A confirmatory lab test can help in appropriate diagnosis and
treatment of severe, intractable infections. 30 Specific diagnosis
of rotavirus infection is made by the identification of virus in the
stool samples using enzyme-linked immunosorbent assay (ELISA)
or immunochromatography. ELISA offers 70–80% sensitivity and
71–100% specificity. 31, 32 Reverse transcription polymerase chain reaction (RT-PCR)
assays are sensitive and allow genotyping of virus isolates. These
tests may also facilitate epidemiological studies. 4 Additional
methods of detection include electron microscopy, polyacrylamide
gel electrophoresis, antigen detection assays, nucleic acid
hybridization, sequence analysis, and virus isolation. 30

Many patients, particularly those born premature, show a mild
increase in blood levels of alanine aminotransferase (ALT) and
aspartate aminotransferase (AST), suggesting that they may have
rotavirus-induced mild hepatitis. 4 These infants with severe disease
may need additional evaluation with abdominal x-ray, blood gas
delec fe totes, blood urea nitrogen, serum creatinine levels, and
complete blood counts.

**Differential Diagnosis**

The differential diagnosis for rotavirus infection can be broad and
include a variety of viral, bacterial, and parasitic causes including
acute abdominal pathologies. 23
Viruses that mimic acute gastroenteritis similar to that of rotavirus include norovirus, adenovirus, and astroviruses. As more than 5% of stool cultures test positive for nonviral etiologies, viruses are sought to be the most common cause of acute infectious diarrhea.

The most common bacterial causes of gastroenteritis are Shigella, Salmonella, Campylobacter, Escherichia coli, Yersinia, Vibrio, Listeria, and Clostridium difficile. Infants with bacterial infections need careful observation because of the risk of sepsis.44

Infants in tropical countries also need to be evaluated for infection with parasites such as Giardia, Cryptosporidium, Cyclospora, Isospora, and Mycobacterium species. Abdominal pathologies and noninfectious extraintestinal causes may also need to be considered in any case of acute diarrhea.44

### Treatment

No specific treatment is yet available for rotavirus infections. Although the disease is self-limiting in many cases, it can cause considerable morbidity in infants, particularly those born premature or are in the age range of 3–24 months. At present, the treatment of rotavirus infection is mainly supportive.

In tropical, remote areas, careful observation for dehydration and oral rehydration therapy is indicated in infants with mild or moderate dehydration. The World Health Organization (WHO)-recommended formula for oral rehydration solutions (ORS) consists of an isotonic salt solution supplemented by glucose (Table 2).35 Since 2005, a reduced-osmolarity ORS preparation has shown therapeutic effectiveness (Table 1).35

In low-resource settings, alternative methods for maintaining hydration have been tried. One example is the resolution prepared by mixing 50 g of rice powder in 1 L of water and boiling the solution (rice water therapy). However, such therapies are frequently difficult to administer and may not be as effective as ORS formulations.37,38

Patients with severe dehydration or in cases where oral rehydration is not possible, need intravenous fluids which can consist of Ringer’s lactate solution, normal saline, or a similar solution.39,40 In some situations where intravenous administration of fluids is not available, there may be a need for alternative, relatively extreme solutions such as subcutaneous hypodermoclysis.51,42 The indications for hospitalization are summarized in Table 3.

The severity of diarrhea has been linked with the nutritional status of the patient. There is a need for adequate caloric intake for recovery, which can be difficult in infants with severe diarrhea.53 Severe zinc deficiency is also a risk factor for adverse outcomes in developing countries,44 and although not specific, there may be some additive benefit with zinc supplementation.45–47 In low-income countries, prophylactic vitamin A supplementation may also reduce rotavirus-related mortality in children >6 months of age.48–50 Vitamin A could possibly strengthen the innate immune defense system and gut integrity.50

Immunocompromised children may need rotavirus specific immunoglobulin preparation. In a study by Guarino et al., children receiving a single dose of 300 mg/kg of orally administered human immunoglobulin showed statistically significant clinical improvement compared to placebo arm. Rotaviral diarrhea in children who received immunoglobulin lasted for 76 hours; the diarrhea lasted an average 131 hours in the group receiving placebo.51

Multiple antiviral drug therapies have been studied for the treatment of rotavirus diarrhea. Nitazoxanide, an antiviral agent that interferes with viral morphogenesis, has been found to reduce the total duration of hospitalization and diarrhea among children. Other potential drugs against rotavirus diarrhea are racemicadotril, clioquinol, and smectite. These therapies have not been extensively studied in neonates and combinations of more than one drug have not been tried. Most standard drug regimens for viral diarrhea do not include drugs. The safety of these agents in young infants still needs to be proven. Antiemetic agents like metoclopramide, ondansetron, and dimenhydrinate are “possibly recommended” in rotavirus diarrhea—they can reduce the need for hospitalization and intravenous fluid therapy.54

### Prevention

Administration of the rotavirus vaccine is the most effective way to prevent rotavirus gastroenteritis in children. The use of rotavirus vaccines should be part of a comprehensive strategy to control rotavirus infections with preventative (promotion of early and exclusive breastfeeding for 6 months, vitamin A and zinc supplementation, hand-washing, improved water supply, and sanitation) and treatment measures.55

Breastfeeding has been found to have an equivocal relationship with the prevention of diarrhea. Some studies have found that exclusive breastfeeding among infants can prevent rotavirus diarrhea which may be attributed to rotavirus IgA antibodies and trypsin inhibitors in breast milk.56,57 Studies have also suggested that breastfeeding can augment the effects of the rotavirus vaccine. But a study conducted by Misra et al. in a country with a heavy disease burden did not find any significant impact of breast feeding on prevention of rotavirus infection.58 A meta-analysis conducted to assess the correlation between breastfeeding and

### Table 2: ORS solutions developed by WHO35

<table>
<thead>
<tr>
<th>ORS solution</th>
<th>Glucose (mmol/L)</th>
<th>Na (mmol/L)</th>
<th>K (mmol/L)</th>
<th>Cl (mmol/L)</th>
<th>Base (mmol/L)</th>
<th>Osmolarity (mosm/L)</th>
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<tr>
<td>WHO 2005</td>
<td>75</td>
<td>75</td>
<td>20</td>
<td>65</td>
<td>10</td>
<td>245</td>
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<tr>
<td>WHO 2002</td>
<td>75</td>
<td>75</td>
<td>20</td>
<td>65</td>
<td>30</td>
<td>245</td>
</tr>
<tr>
<td>WHO 1975</td>
<td>111</td>
<td>90</td>
<td>20</td>
<td>80</td>
<td>30</td>
<td>311</td>
</tr>
</tbody>
</table>

### Table 3: Indications for hospitalization of children include52,53

- Shock
- Severe volume depletion
- Moderate volume depletion with refusal of oral fluids
- Clinical deterioration
- Intractable or bilious vomiting
- Failure of oral rehydration
- Neurologic abnormalities (e.g., lethargy, seizures)
- Possibility of severe illness or condition other than acute gastroenteritis that requires specific therapy (e.g., bowel obstruction)
rotavirus infection, too, did not find the role of breastfeeding to be effective in prevention.\textsuperscript{59}

The role of supplemental zinc in the prevention of acute diarrhea has proven to be quite effective. The analysis of randomized, controlled trials of zinc supplementation performed in nine low-income countries from Latin America and the Caribbean, South and Southeast Asia, and the Western Pacific suggested an 18% reduction in the incidence of diarrhea and a 25% reduction in the prevalence of diarrhea.\textsuperscript{60}

Improved hand hygiene has been found to reduce the incidence of acute gastrointestinal diseases by 31% (95% confidence interval, 19–42). Despite reducing the incidence of gastroenteritis, another study found that hand hygiene had little effect on disease transmission.\textsuperscript{61,62}

The major complication of rotavirus infection in infants and young children is dehydration, which can lead to electrolyte imbalance, metabolic acidosis and eventually circulatory collapse and death in the most severely-affected cases.

\textbf{Vaccination}

Endeavors to develop effective vaccines against human rotaviruses began as early as the 1980s.\textsuperscript{3} Rotavirus vaccines are attributed to prevent 15–34% of severe diarrhea in third world countries and 37–96% of severe diarrhea in developed countries. It is estimated that vaccines have saved more than 28,000 lives (95% CI 14,600–46,700) in sub-Saharan Africa.\textsuperscript{65}

There are four vaccines available for protection against rotaviruses (Table 4). The first vaccine against rotavirus—RotaShield of RRV-TV—was found to be highly effective (80–100%) in preventing severe diarrheal illness. After administration in 600,000 infants in the United States, RRV-TV was stopped in July 1999 when it was found to be associated with an 25-fold increased relative risk of intussusception within the first 10 days of administration.\textsuperscript{3} In the 7 years of vaccine hiatus, as newer alternatives were explored, rotavirus-related diarrheal illness continued to cause significant mortality and mortality.

In 2006, two new vaccines—Rotateq (a reassorted bovine-human rotavirus) and Rotarix (derived from a single common strain of human rotavirus). These vaccines were found to be safe and not associated with intussusception, in fact, the recipients of these vaccines had lower incidence of intussusception.\textsuperscript{3}

- Infants who are born preterm should be immunized according to their chronological age. A study showed no increase in adverse events following vaccination in premature infants.\textsuperscript{69}
- Ninety-two countries had incorporated rotavirus vaccine into their national immunization programs by the year 2018; six other countries introduced rotavirus on a phased or regional basis.\textsuperscript{66}

The rotavirus vaccination drive met with a challenge in 2018 and 2019 due to its short supply which led to the efforts of development of newer vaccines—Rotavac (naturally occurring bovine-human reassortant neonatal G9P, also called 116E); and RotaSiil (bovine-human reassortant with human G1, G2, G3, and G4 bovine UK G6P5 backbone). These new vaccines are currently used in Palestine (Rotavac) and India (both vaccines).

WHO recommends the incorporation of rotavirus vaccination in all national immunization programs, particularly in countries with high risk of disease severity and mortality. It is estimated that in Asia alone vaccination could potentially save the lives of 109,000 children, prevent 1.4 million hospital admissions, 7.7 million OPD visits; it can decrease the healthcare cost by US$ 191 million.\textsuperscript{67}

Despite four WHO-prequalified oral rotavirus vaccines available, and several newer vaccines under development, the global disease burden of rotavirus continues to impose a challenge.\textsuperscript{68} Many countries are yet to introduce rotavirus vaccines in their national immunization schedule. With a favorable risk-benefit profile and proven clinical efficacy demonstrated in most parts of the world, vaccination appears to be the most effective way to curb this illness.

\textbf{Prognosis}

Rotavirus infection has a considerable public health burden. In the prevaccine era, rotavirus was the nearly universal infection of children by age 5 years and was responsible for up to 500,000 deaths worldwide.\textsuperscript{63} After the introduction of the vaccine, globally, it is estimated that the number of rotavirus deaths in children <5 years of age declined from 528,000 (range, 465,000–591,000) in 2000–2015,000 (range, 197,000–233,000) in 2013.\textsuperscript{64} The substantial decline in diarrhea mortality over the past decade can also be

\textbf{Table 4: Rotavirus vaccines}

<table>
<thead>
<tr>
<th>Composition and strains</th>
<th>Rotateq</th>
<th>Rotarix</th>
<th>Rotavac</th>
<th>Rotasil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administration</strong></td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dose regimen</strong></td>
<td>3—at 2, 4, and 6 months of age</td>
<td>2—at 2 and 4 months of age</td>
<td>3—at 6, 10, and 14 weeks</td>
<td>3—at 6, 10, and 14 weeks</td>
</tr>
<tr>
<td><strong>Protection against severe disease</strong></td>
<td>85% (72–92)</td>
<td>95% (91–97)</td>
<td>53.6%</td>
<td>33.6–66.7%</td>
</tr>
<tr>
<td><strong>Virus shedding</strong></td>
<td>9%</td>
<td>≥50%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Intussusception</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>% Reduction in hospitalization</strong></td>
<td>63</td>
<td>42</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td><strong>First licensure date</strong></td>
<td>Licensed in the USA and Europe in 2006</td>
<td>First approved in Mexico in 2004</td>
<td>Licensed in India in 2014</td>
<td>Licensed in India in 2006</td>
</tr>
<tr>
<td><strong>WHO prequalification date</strong></td>
<td>October 7, 2008</td>
<td>March 12, 2009</td>
<td>January 5, 2018</td>
<td>September 21, 2018</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Liquid</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Lyophilised active component</td>
</tr>
</tbody>
</table>
largely attributed towards general improvements in sanitation and hygiene.

**Complications**

Rotavirus infection in infants has been found to be associated with pneumonia, necrotizing enterocolitis (NEC), sudden infant death syndrome (SIDS), encephalitis, seizures, bradycardia-apnea, and diffuse intravascular coagulopathy (DIC). Rotavirus infection, especially in premature babies, may be associated with necrotizing enterocolitis and secondary bacteraemia. Immunocompromised children owing to congenital immunodeficiency or bone marrow or solid organ transplantation may experience persistent infection lasting weeks or months. They may develop abnormalities in multiple organ systems, particularly the kidney and liver.

Approximately, 2–3% of children suffer from neurological complications, most common manifestation being febrile or afebrile seizures. In rare cases, rotavirus have also been implicated in the causation of meningoencephalitis, cerebellitis, and encephalopathy. Rotavirus infection has also been associated with aseptic meningitis, sudden infant death syndrome (SIDS), and Kawasaki syndrome.

**Epilogue**

Rotavirus gastroenteritis causes substantial child mortality and morbidity worldwide, with almost 80% of deaths occurring in developing countries. Rotavirus in neonates although less prevalent than in infants is a topic that’s under studied and requires further studies to understand the differences in the disease incidence, prevalence, and pathogenesis. While infants were prone to get community-acquired infections, neonates, on the other hand, were more likely to acquire nosocomial infections.

The tremendous global burden of this disease emphasizes the urgent need for interventions, such as vaccines, particularly to prevent childhood deaths in developing nations. Administration of the rotavirus vaccine is the most effective way to prevent rotavirus infection along with sanitation and hygiene measures. Rapid progress towards the development of rotavirus vaccines has prompted a reassessment of the disease burden of rotavirus diarrhea in developing countries.

**Author Contribution**

Preeti Shakya and Biplov Adhikari contributed equally to this work.

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