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Acute Gastroenteritis Viruses

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KEY CONCEPTS

- Acute diarrhea is the leading cause of morbidity and second commonest cause of mortality in children <5 years old worldwide.
- Most acute diarrheal illnesses are caused by viruses.
- Noroviruses are the commonest cause of diarrhea in all age groups combined, and rotaviruses are still the leading cause of diarrhea for children <5 years old.
- Transmission is mainly by the fecal–oral route through person-to-person contact, contaminated food and water.
- Most cases of viral diarrhea are mild and self-limiting, but severe cases occur, leading to dehydration and death. Repeated episodes lead to malnutrition.
- Most cases can be managed at home with oral rehydration solutions and feeding a regular diet.
- Vaccines will be the best preventive measure. Only rotavirus vaccines are available.
- Breast-feeding, vitamin A supplementation and zinc significantly reduce the frequency and/or severity of diarrhea.

Introduction

Acute diarrhea is the leading cause of morbidity and second commonest cause of mortality in children aged 0–5 years old. Worldwide estimates for this age group in 2010 were: 1.731 billion cases, with 36 million severe episodes, and 700 000 deaths.[1] For older children, adolescents and adults, the estimate is 2.8 billion cases of diarrhea per year.[2] Viruses account for most of acute diarrhea illness,[3] mainly caliciviruses in all age groups and rotaviruses in children. Morphological, epidemiological and clinical characteristics of the main gastroenteritis viruses are presented in Tables 162.1 to 162.3.

Rotaviruses

Described in 1973 by Bishop *et al.*[4] human rotaviruses (RVs) represent the main agent of acute gastroenteritis in infants and young children worldwide.

Nature

Rotaviruses (RVs) belong to the family Reoviridae.[5] Intact 75 nm particles have a triple-layered structure with a core, and the inner and outer capsid layers. The core encloses the viral genome, consisting of 11 segments of double-stranded RNA. Each segment encodes for one protein, except segment 11 that encodes for two (Figure 162-1, Table 162-4). Six proteins (VP1–VP4, VP6–VP7) form the virion structure. The core is made of VP1, VP2 (its major constituent) and VP3; VP6 is the sole component of the inner capsid; and the outer capsid is composed of VP7 (90%) and VP4. VP4 forms the capsomers, spike-like structures that radiate from the inner to the outer capsid giving the virus its characteristic wheel-like appearance (*rota* = wheel). In addition, six nonstructural proteins (NSP1–NSP6) are expressed in the infected cell and participate in the replicative cycle.[6,7]

VP6 defines eight antigenic groups (A–H)[8] with group A RVs causing most human infections. The outer capsid proteins VP7 and VP4 elicit neutralization antibodies and determine serotypes, respectively designated as G (for glycoprotein), and P (for protease-sensitive protein). Nowadays, serotyping has been largely replaced by genotyping. Rotaviruses are designated with a dual system of G and P letters followed by a number to notate the serotype and a second number in brackets after P for the genotype, or – more frequently now – a genotype-only designation. For example, the human RV strain Wa is designated G1P1A[8] or G1P[8]. There are at least 27 G and 37 P genotypes.[9]

Epidemiology

Transmission of RVs is mainly from person-to-person by the fecal–oral route.[10] Spread is favored by the large number of virions excreted in feces (~1×10^{12} per mL) and the low infective dose (~1×10^{4} RV particles).[11] Asymptomatic shedding is frequently detected, especially among young children.[12] Fecal excretion starts immediately before the onset of symptoms and lasts for 5–7 days;[13] longer as detected by polymerase chain reaction (PCR).[14] Outbreaks have been described in nursing homes, hospitals and military bases, with food or water contamination implicated in some outbreaks.[7] Since RVs can survive for 60 days on environmental surfaces,[15] fomites may play a role in settings such as daycare centers and nurseries. RVs have been detected in 20% of cases of travelers' diarrhea.[16] The role of respiratory transmissions is controversial and likely of limited importance.[17]

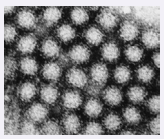
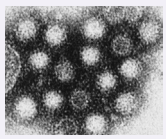
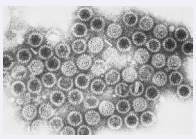
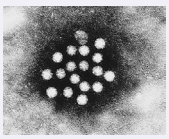
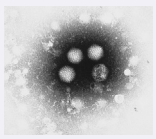
RVs are the most commonly identified viral enteropathogens of infants and young children worldwide[18] – especially for severe diarrhea. In the USA, before vaccination, RVs caused 3.5 million cases, 55 000 hospitalizations, 20–40 deaths and costs of $1 billion annually.[19] Worldwide, the annual estimates were 111 million episodes, 2 million hospitalizations and 600 000 deaths.[20] Most affected are children under 5 years of age, with incidence rates peaking at 6–24 months old. Neonates are affected infrequently, and exposed adults become infected frequently (11–70%) but rarely develop clinical disease.[21,22] RVs present as characteristic winter epidemics in North America, marching from the southwest to the northeast.[23] In tropical climates, RVs are endemic throughout the year, with some clustering in the cooler, drier months.

Globally, group A types G1–G4 and G9, in conjunction with P[8] or P[4], constitute most human infections, the most common combination being G1P[8]. However, there is much geographic and temporal variability.[6,24] Multiple types can co-circulate during a specific year.

Pathogenicity

The replication cycle of RV has been reviewed elsewhere.[7] RVs preferentially infect the mature enterocytes of the small intestine. VP4 attaches to sialic acid residues or oligosaccharides of the histo-blood group family on the host cell. Individuals lacking a functional *FUT2* gene (about 20% of the white population) appear resistant to RV infection.[25] VP4 is cleaved into VP5* and VP8* by host proteases initiating the infection. The virus enters enterocytes either by direct membrane penetration or by receptor-mediated endocytosis.[26] Intracellular Ca^{2+} levels trigger virus uncoating and RNA synthesis proceeds in the core of the virion, mediated by VP1.[27,28] RV proteins are synthesized utilizing the host cell translational machinery. The initial steps of virus replication occur in cytoplasmic inclusions. The viral subparticles bud through the membrane of the endoplasmic reticulum and become

TABLE 162-1 Structure and Morphological Characteristics of Gastroenteritis Viruses

Characteristics	Norovirus	Sapovirus	Rotavirus	Astrovirus	Enteric Adenovirus
Family	Caliciviridae	Caliciviridae	Reoviridae	Astroviridae	Adenoviridae
Virion size (nm)	27–35	27–40	70–75	41	70–80
Envelope	Non-enveloped	Non-enveloped	Non-enveloped	Non-enveloped	Non-enveloped
Capsid	Icosahedral	Icosahedral	Triple shelled	Icosahedral	Icosahedral
Genome type	Positive-sense ssRNA	Positive-sense ssRNA	Segmented dsRNA	Positive-sense ssRNA	dsDNA
Morphology on electron microscopy	Round surface, cup-shaped indentations	Round surface, cup-shaped indentations	Wheel-like capsid with radiating spokes	Round, 28–30 nm, 5–6-pointed star shape	Fiber-like projections from vertices
Electron micrograph					

ds, double-stranded; ss, single-stranded.
Norovirus and sapovirus electron micrographs courtesy of C. Humphrey, (CDC). Rotavirus, astrovirus and enteric adenovirus electron micrographs, courtesy of S. Spangenberger.

TABLE 162-2 Epidemiological Characteristics of Gastroenteritis Viruses

Characteristic	Norovirus	Sapovirus	Rotavirus	Astrovirus	Enteric Adenovirus
Age group	All ages	Children	6–24 months	<7 years, elderly	<4 years
Seasonality	Winter	No	Winter	Winter	Summer
Disease pattern	Outbreaks, endemic	Endemic, outbreaks	Endemic, annual epidemics	Endemic, nosocomial outbreaks	Endemic
Transmission	Person-to-person, water, food, shellfish	Person-to-person, water, cold foods, shellfish	Person-to-person, food, water	Person-to-person, food, water	Person-to-person
Fecal excretion (days)	13–56 Median: 28	–	10	–	Persistent, months
Outpatient prevalence (%)	Endemic: 10–25 Outbreaks: 90	1–10	5–10	7–8	4–8
Inpatient prevalence (%)	Frequent	3–5	35–40	3–5	5–20

TABLE 162-3 Usual Clinical Characteristics of Gastroenteritis Virus Infections

Signs and Symptoms	Norovirus	Sapovirus	Rotavirus	Astrovirus	Enteric Adenovirus
Prodrome (days)	1–2	1–3	1–3	3–4	8–10
Diarrhea: watery	66–95% 4–8/day Adults >children	88–95% mild	96–100% 10–20/day	72–100% 2–4/day	97% 1/3 >14 days
Vomitus	57–95% Children >adults	44–65%	80–90% Early	20–50% 1/day	79% Early
Fever	24–48% Low grade	18–34%	60–65% Moderate	20% Low grade	Occasionally Low grade
Abdominal pain	11–91% cramps	–	Colicky	50%	–
Dehydration	~1%	Infrequent	Frequent in young children	Infrequent	Infrequent
Other symptoms	Myalgia 26%, headache 22%	Respiratory 22%, myalgia, headache	Respiratory 22–52%	Malaise, respiratory	Respiratory occasionally
Duration of illness (days)	0.5–2.5	4	3–8	2–3	5–12

mature particles. NSP4 plays a key role in the assembly process of these particles, which is Ca^{2+} dependent. Lastly, mature viruses are released by cell lysis or by vesicular transport.[7]

Infected intestinal cells change from columnar to cuboidal, with fewer and shorter microvilli; the cells are sloughed off resulting in shorter villi. Changes occur within 24 hours of infection, start proximally and progress caudally.[4,29] Diarrhea results from a mixture of causes: decreased absorption of salt and water secondary to enterocyte damage and replacement of absorptive intestinal cells by secreting cells from the crypts; loss of disaccharides at the damaged brush border

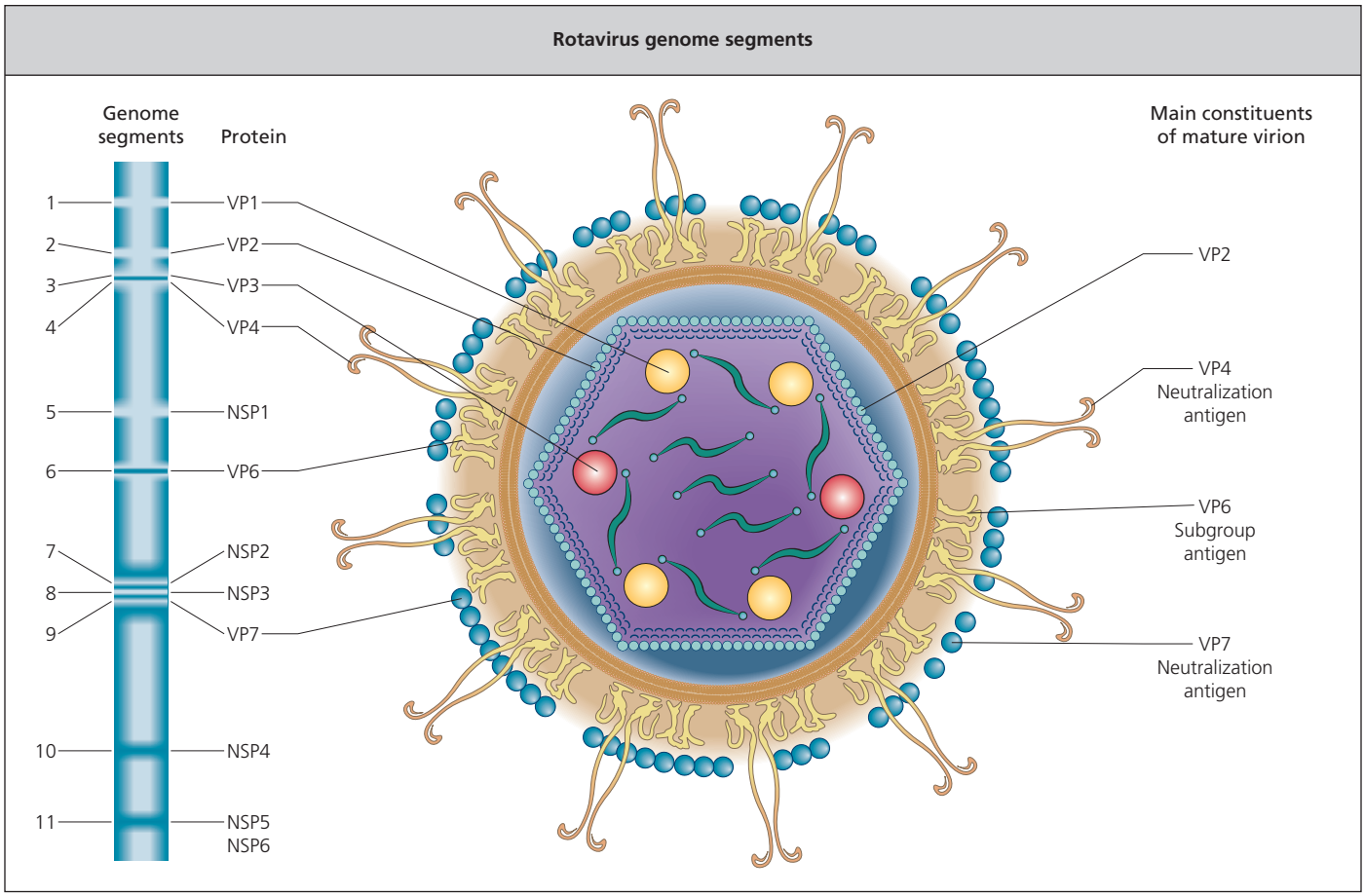


Figure 162-1 Rotavirus genome segments, protein products and their location in the viral particle. *(Adapted with permission from Gentsch J.R., Laird A.R., Bielfelt B., Griffin D.D., Banyai K., Ramachandran M., et al. Serotype diversity and reassortment between human and animal rotavirus strains: implications for rotavirus vaccine programs.* J Infect Dis *2005; 192 (Suppl 1):S146-59.)*

TABLE 162-4 Rotavirus Genome Segments and Their Corresponding Viral Proteins

Genome Segment (Size, Bp)	Protein Product (MW, Kda)	Location in Virus Particles	Function
1 (3302)	VP1 (125)	Core capsid	RNA-dependent RNA polymerase, complex with VP3
2 (2729)	VP2 (94)	Core capsid	Main constituent of core, RNA binding
3 (2591)	VP3 (88)	Core capsid	Complex with VP1, guanylyl and methyl transferase, synthesis of capped mRNA transcripts
4 (2359)	VP4 (86.7)	Outer capsid	Hemagglutinin, cell attachment, neutralization antigen, determines P serotypes, cleaved by trypsin into VP5*(52.9) and VP8*(24.7) virulence
5 (1566)	NSP1 (58.6)	Nonstructural	Basic protein, RNA binding
6 (1356)	VP6 (44.8)	Inner capsid	Main constituent of inner capsid, determines group specificity, protection, required for transcription
7 (1074)	NSP3 (34.6)	Nonstructural	Acidic protein, RNA binding, inhibits host cell translation
8 (1059)	NSP2 (36.7)	Nonstructural	Basic protein, RNA binding, forms viroplasms with NSP5
9 (1062)	VP7 (37.4)	Outer capsid	Glycoprotein, major constituent of outer capsid, determines G serotypes
10 (750)	NSP4 (20.2)	Nonstructural	Role in morphogenesis, interacts with viroplasms, modulates intracellular Ca^{2+} and RNA replication, enterotoxin, virulence
11 (664)	NSP5 (21.7)	Nonstructural	Role in morphogenesis, forms viroplasms with NSP2, interacts with VP2 and NSP6
11 (664)	NSP6 (12)	Nonstructural	Interacts with NSP5, present in viroplasms

Bp, base pairs; MW, molecular weight.
Adapted with permission from Estes M.K., Kapikian A.Z. Visualization by immune electron microscopy of a 27 nm particle associated with acute infectious nonbacterial gastroenteritis. J Virol *1972; 10:1075-81.*

resulting in carbohydrate malabsorption and osmotic diarrhea; and the effect of NSP4, a viral enterotoxin that increases plasma membrane chloride permeability leading to secretory diarrhea.[30] RV RNA and replicating viruses are frequently detected in blood and cerebrospinal fluid,[31] showing that RV represents a systemic infection with increase of pro-inflammatory cytokines.[32]

Immunity against RVs is likely multifactorial; involving local (mucosal) and systemic (serum) antibodies as well as innate and cellular immunity.[33,34] VP7 and VP4 induce serum-neutralizing antibodies against the infecting serotype (homotypic) that appear within 2 weeks of infection and correlate with protection.[21] Heterotypic antibodies (those against different serotypes) also occur, but mainly among adults and are dependent on the infecting strain. Homotypic protection lasts longer than heterotypic protection but is incomplete and short lived.[21] Anti-RV antibody levels are high at birth (transplacentally acquired), decline by 3–6 months, rise to a peak at 2–3 years and remain elevated throughout life (probably because of repeated, mostly asymptomatic infections).[35] Serum antibodies do not always prevent infection, pointing to the potential role of mucosal immunity. For example, IgA deficient mice shed RV for a prolonged time and are not protected against reinfection.[31] Furthermore, mucosal immunity, passively acquired by breast-feeding[36] or by orally administered immune globulins[37] ameliorates RV symptoms. Mucosal immunity develops 4 weeks after infection and persists for several months, eventually decreasing with advancing age.[38] Experimental and clinical data suggest a role for non-neutralizing anti-VP6[39-41] and other antibodies[42] in protection against RV disease. Cell-mediated immunity also seems important. In mice, RV-specific cytotoxic T cells appear in the intestinal mucosa soon after infection, and mice with severe combined immunodeficiency are able to clear RV infection when reconstituted with CD8 T cells, despite their lack of antibodies against the virus.[43] Lastly, the role of innate immunity is being explored.[44]

Clinical Manifestations

The clinical spectrum of RV infections ranges from asymptomatic to severe disease with dehydration and death; severity may be associated with antigenemia.[45] The usual clinical picture is presented in Table 162-3; in addition, transaminase elevation occurs in about 15% of cases[46] and neurological manifestations are increasingly recognized.[47] The disease is self-limiting and chronic infection has not been described in the normal host.[35] Neonatal RV infections are symptomatic in only 10–20% of cases and usually mild,[48] but severe infections may occur among premature infants and those in special care units.[49] Immunodeficient individuals can present a chronic or serious course with associated mortality.[50] Children with human immunodeficiency virus (HIV) infection, and not receiving antiretroviral therapy, may have a twofold risk of RV symptomatic infection and more prolonged virus shedding, but the severity of the illness itself may be similar to that seen in HIV-uninfected children.[51,52]

Diagnostic Microbiology

Antigen detection kits based on enzyme immunoassays (EIAs) and latex agglutination are the tests of choice for most clinical circumstances with high sensitivity and specificity (70–100%). Samples should be obtained during the symptomatic period. If samples are not to be processed immediately, they can be stored at 39.2°F (4°C) or frozen. A semi-nested reverse transcription polymerase chain reaction (RT-PCR) test allows for G and P genotyping.[53] In special situations, other tests can be considered: electron microscopy (EM), gel electrophoresis of viral RNA, hybridization of radiolabeled nucleic acid probes and viral culture. Serologic tests are rarely used. Neutralizing antibodies can be detected by plaque reduction or cytopathic effect inhibition.

Caliciviruses: *Norovirus, Sapovirus*

In 1972, Kapikian *et al.*, investigating a gastroenteritis outbreak in Norwalk, Ohio, visualized 27 nm particles in a stool filtrate and noted that infected individuals developed specific antibody response against the particles. The particles were named Norwalk virus (NV). This was the first confirmation of a virus as an etiological agent of gastroenteritis.[54] Similar viruses were named by the location where they were first identified (Hawaii, Sapporo, etc.) and, as a group, were known as Norwalk-like viruses or small round structured viruses (SRSVs). Cloning of the NV genome led to the classification of these viruses within the Caliciviridae family.[55]

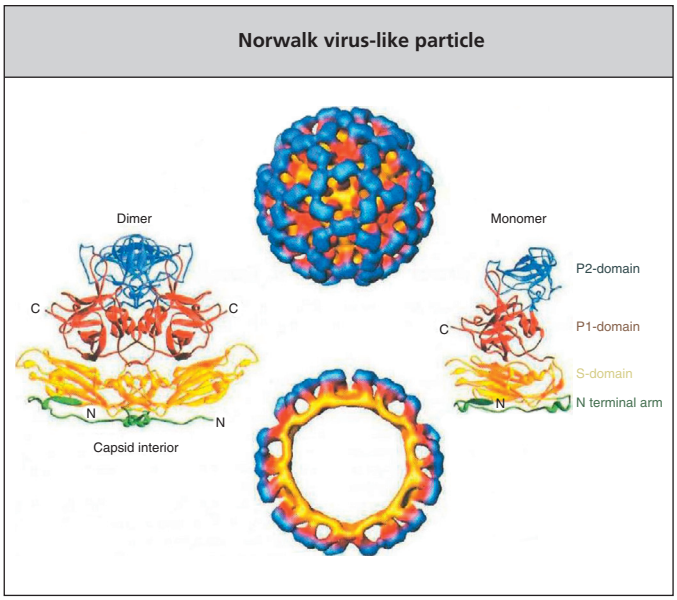


Figure 162-2 Norwalk virus-like particle. *(Adapted from Hutson* et al. Trends Microbiol *2004; 12:279–87, with permission.)*

Nature

Caliciviruses (CV) are small (27–40 nm), non-enveloped viruses with a single-stranded positive-sense RNA genome. They have an icosahedral capsid with cup-like depressions on the viral surface (*calici* is derived from the Latin word *calyx* = cup) (Figure 162-2).

Five genera have been identified in the Caliciviridae family: *Lagovirus, Nebovirus, Vesivirus, Norovirus* (NoV) and *Sapovirus* (SaV). *Lagovirus, Nebovirus* and *Vesivirus* only infect animals. NoV and SaV have human and animal strains and are further classified into genogroups, genotypes (genetic clusters) and subgenotypes or variants (Table 162-5).[5,56] Both NoV and SaV produce diarrheal illness in humans and NoV is the leading cause of acute gastroenteritis worldwide.

The CV genomes are about 7.3–8.5 kilobases in length and organized in two or three open reading frames (ORFs). In the genera with three ORFs (NoV and *Vesivirus*) the first ORF (ORF1) encodes for a large protein that by proteolytic cleavage produces the NSPs. The ORF2 encodes for the single major structural protein (VP1), and the ORF3 encodes for a minor structural protein (VP2). The *Nebovirus* and *Lagovirus* have only 2 ORFs. In these viruses, VP1 and VP2 are encoded in ORF1 and ORF2, respectively.[56]

A typical CV (Norwalk virus) capsid is formed by 90 VP1 dimers with 90 arch-like protruding capsomers arranged in such a way as to leave 32 calices on the viral surface. The VP1 has two major domains: the shell (S) domain and the protruding (P) domain. The S domain forms the inner part of the capsid. It has 225 amino acids (aa), including aa 10-49 corresponding to the N terminal region of the protein (N subdomain), which faces the interior of the capsid. The P domain includes amino acids 226–520 and is subdivided into subdomains P1 and P2. The P1 subdomain (aa 226–278 and 406–520) form the sides of the capsomers whereas the P2 subdomain (aa 279–405) form the most protruding part of the capsomers' arch (Figure 162-2). Each virion has only one or two copies of the VP2 (~22–29 kDa). The VP2

TABLE 162-5 Taxonomy of the Caliciviridae Family

Genus	Genogroups	Genetic Clusters	Representative Species	Representative Strain*
Norovirus (NoV)	I	1–8	Norwalk virus	Hu/NoV/GI.1/Norwalk/1968/US
	II	1–19	Hawaii norovirus	Hu/Nov/GII.1/Hawaii/1971/US
	III	1–2	Bovine norovirus	Bo/NoV/GIII.1/Jena/1980/DE
	IV	1	Alphatron virus	Hu/Nov/GIV.1/Alphatron98-2/1998/NL
	V	1	Murine norovirus	M/NoV/GV.1/MNV-1/2003/US
Sapovirus (SaV)	I	1–3	Sapporo virus	Hu/SaV/G1.1/Sapporo/1982/JP
	II	1–3	London sapovirus	Hu/SaV/GII.1/London/1992/UK
	III	1	Swine sapovirus	Sw/SaV/GIII.1/PEC-Cowden/1980/US
	IV	1	Houston sapovirus	Hu/SaV/GIV.1/Hou7-1181/1990/US
	V	1	Argentina sapovirus	Hu/Sav/GV.1/Argentina 39/AR
Lagovirus (LaV)			Rabbit hemorrhagic disease virus	Ra/LaV/RHDV/GH/1988/DE
			European brown hare syndrome virus	Ha/LaV/EBHSV/GD/1989/FR
Vesivirus (VeV)			Vesicular exanthema of swine virus	SW/VeV/VESV/A48/1948/US
			Feline calicivirus	Fe/VeV/FCV/F9/1958/US
Nebovirus (NeV)			Newbury 1 virus	Bo/BV/Newbury-1/1976/UK

Host species abbreviations: Bo, bovine; Fe, feline; Ha, hare; Hu, human; M, murine; Ra, rabbit; Sw, swine.
Country abbreviations: AR, Argentina; DE, Germany; FR, France; JP, Japan; NL, Netherlands; UK, United Kingdom; US, United States.
*Host species/genus/species or genogroup/strain name/year of occurrence/country of origin.
Adapted with permission from Green et al. J Infect Dis *2000; 181:5322-5330.*

function is not completely understood; it appears to interact with the genome RNA during virus replication.[57] VP1 and VP2 self assemble into virus-like particles (VLPs) without RNA participation. VP2 is not needed for VLPs assembly but is essential for infections in feline calicivirus. The VLPs are morphologically and antigenically similar to natural virions.[58] The NoV has six nonstructural proteins with different functions: NSP 1/2 (p48), replication complex formation; NSP3 (NTPase), nucleoside triphosphatase/RNA helicase; NSP4 (p22), replication complex formation; NSP5 (VPg), genome linked protein involved in translation and replication; NSP6 (3CL, Pro), protease; and NSP7 (Pol, RdRp), RNA-dependent RNA polymerase. They play a role in the replication process of the genome RNA.[57,59]

Epidemiology

Human caliciviruses (HuCV) have worldwide distribution, and NoV infects persons of all ages, both in high-income and low- and middle-income countries (LMIC).[60] They are the most common cause of gastroenteritis outbreaks, and they are also recognized as the most common cause of endemic gastroenteritis.[61] In the USA, NoV produces 400 000 emergency department visits and 1.7 million office visits per year;[62] it also accounts for 19–21 million illnesses, 56 000–71 000 hospitalizations and 570–800 deaths.[63] Norovirus is the most commonly detected pathogen (26%) in adults with gastroenteritis.[64,65] In a 2009–2010 study of children under 5 years of age with acute gastroenteritis, RV and NoV were detected in 12 and 21 of the cases, respectively. The study conclusion is that 'norovirus has become the leading cause of medically attended gastroenteritis in US children' being responsible for approximately 1 million healthcare visits yearly.[66]

Norovirus infections occur mainly during the cold seasons. Almost 80% of cases and 71% of outbreaks occur from October to March in the northern hemisphere and from April to September in the southern hemisphere. The reasons for seasonality are not well understood but rainfall may play a role. Breaks in seasonality pattern have been observed with the emergence of new variant strains.[67]

Norovirus infections start early in life; a Finnish study found that the prevalence of GII-4 IgG antibodies was 47% in children aged 7–23 months and 91% after 5 years of age.[68] A birth cohort study in Peru followed 220 and 189 children for 1 and 2 years, respectively. By 1 year 80% of the children had at least one norovirus infection and by 2 years 71% had one or more episodes of norovirus-associated diarrhea.[69] Genogroups I and II strains produce the majority of infections. At a given time, most infections are caused by a major circulating strain. For example, after 2000, GII genogroup caused 96% of sporadic infections in children worldwide[70] and genogroup II.4 strains has caused more than 80% of US outbreaks since the 1990s.[71] Coinfections with different strains occur, giving the opportunity for the exchange of genetic material between strains and the generation of new virus variants.[72] Pandemic variants emerge every 2–4 years. Outbreaks occur mainly in daycare centers, schools, colleges, hospitals, nursing homes, military barracks, restaurants, vacation facilities and cruise ships. NoV also causes travelers' diarrhea. NoV can spread internationally through contaminated food or beverages.[73] A study of 8271 food-borne outbreaks of gastroenteritis showed a median of affected persons of 25 versus 10 for the bacterial outbreaks. Ten percent of the individuals required medical care and 1% were hospitalized.[74]

Sapovirus epidemiology is summarized in Table 162-2. Detection rates vary for different countries, and are much lower than those of NoV and illness is milder. Environment, eating habits and hygiene practices likely play a role in the different attack rates.[75]

Caliciviruses are ubiquitous and stable in the environment, providing a persistent source of infection. Noroviruses survive freezing, heating to 60°C (140°F) for 30 minutes and are stable in water chlorinated to 6.25 mg/L; most municipal water systems contain <5 mg/L of chlorine. The virus is also acid-resistant and ether-stable.[76,77] Caliciviruses are transmitted by the fecal–oral and vomit–oral routes. Sporadic and outbreak cases are spread mainly by person-to-person contact; the patients are more contagious during the first few days of illness. Contaminated food or water are important causes of outbreaks. Transmission through contaminated objects or surfaces in the environment is likely important and may last 2 weeks or longer.[78] Inhalation and swallowing of aerosols produced by vomiting or toilet flushing may also play a role in norovirus spread.[79]

Pathogenicity

The 50% human infectious dose is 1320 genome equivalents.[80] The median incubation period is 1.2 days, 5% of patients develop symptoms in 0.5 days and 95% of them will be symptomatic in 2.6 days.[81] Studies of NoV infections in volunteers described pathological changes in the proximal portions of the small intestine with broadening and blunting of the villi, crypt cell hyperplasia, cytoplasm vacuolization and mononuclear cell infiltration in the lamina propria. Brush border enzymes are decreased, producing malabsorption of carbohydrates and fat. The changes are transient and resolve within 2 weeks.[82,83] No histological lesions are seen in the gastric or rectal mucosa, and the secretion of hydrochloric acid, pepsin and intrinsic factor remain normal.[84] Gastric emptying is markedly delayed, which could explain the frequency of nausea and vomiting; however, the degree of delay does not correlate with the severity of vomiting.[85] Reduction of villous surface area, and sealing junctional proteins as well as increased active anion secretion, cytotoxic intraepithelial lymphocytes and apoptosis, have been observed suggesting that norovirus diarrhea is caused by a leak flux and secretory component.[86] Virus shedding in the stools begins during the prodrome stage, lasts 13–56 days (median 28 days)[87] and it can persist for several weeks after resolution of symptoms, especially in infants and for months to years in immunocompromised patients.[88,89]

Norovirus infection starts when the protruding domain (P) of the VP1 binds specific carbohydrate receptors on the cell membrane; thereafter NoV enters the cell by a process that requires a protein receptor. This is followed by virus uncoating and release of VPg-linked RNA genome to the cytoplasm. Genome replication starts with a negative-sense RNA intermediate. This process is performed by NSP7 (RdRp). The genome functions as an mRNA for the first viral RNA translation, and becomes a template for a double-stranded replication form (RF). Thereafter positive-sense RNA synthesis begins. During the replication process, full genome and subgenomic RNA are formed. Subgenomic RNA consists of the last 2.4 kb of the genome (ORF2+ORF3), and it is also attached to VPg. The ORF1 generates the polyprotein that after cleavage produces the NSPs. NS1/2 and NS4 recruit cellular membranes to form a replication complex. Both VP1 and VP2 capsid proteins are translated mainly by subgenomic RNA. VP1 self-assembles to form the capsid or VLP. Nevertheless VP2 is required for infectivity. The mechanisms of viral assembly and release of the virions are poorly understood; apoptosis has been proposed as an exit strategy. It is assumed that HuNoV replication occurs in the epithelial cells of the upper gastrointestinal tract; however, no viral particles have been observed by EM of the jejunum mucosa[59,90] (Figure 162-3).

Susceptibility to NV is peculiar. Some individuals have natural resistance to the infection. They lack virus receptors; repeated challenges with the virus fail to produce illness or antibody response. Norovirus receptors are the histo-blood group antigens (HBGAs). HBGAs are complex carbohydrates present on the surface of erythrocytes, enterocytes and other mucosal cells. HBGAs include the ABO, Lewis and secretor families. HBGAs production is genetically controlled. The *FUT2* gene controls the expression of fucosyltransferase 2 in saliva and mucosal secretions. Individuals who do not have the *FUT2* gene are called non-secretors. Twenty percent of Europeans are non-secretors and resistant to infection with the NV. Recognition of carbohydrate receptors is a common characteristic of calicivirus. Different CV have different carbohydrates receptors which determine host and tissue tropism.[91,92]

Norovirus immunity studies are difficult because there is no cell culture system or small animal model. Human volunteer and natural infections studies demonstrate virus-specific antibody response. Serum IgG, IgM and IgA as well as mucosal IgA antibodies are produced. Cell-mediated immunity has been induced by VLP. Serum IgG antibodies persist for months, IgM and IgA are short lived, mucosal IgA persistence is not known.[90,93] Antibody presence does not always correlate with protection; however, early (<5 days) mucosal IgA production protects against infection.[94] Earlier studies suggested that immunity is mostly short-term (6 months–2 years) and type-specific; however, several clinical and epidemiological observations were inconsistent with this notion. Mathematical models of community transmission of norovirus estimated immunity duration for gastroenteritis at 4.1– 8.7 years.[95]

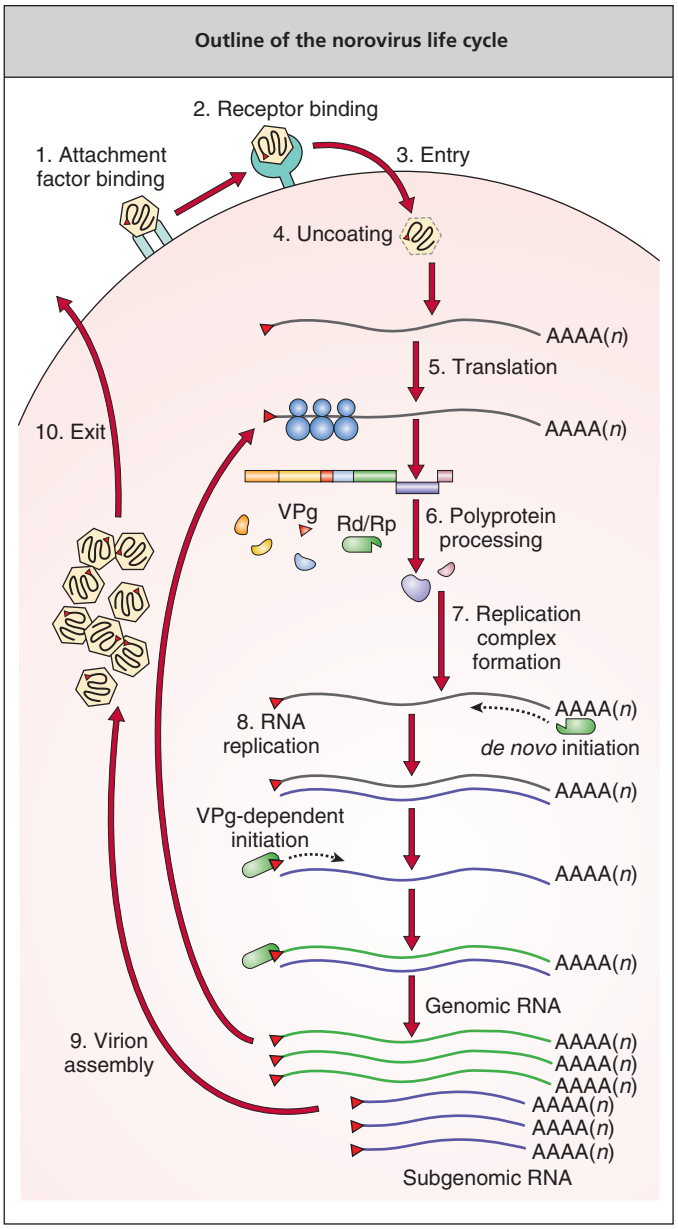


Figure 162-3 Outline of the norovirus life cycle. (1) HuNoV and MNoV are thought to attach to the cell surface using various carbohydrate attachment factors. This is not sufficient to mediate entry, and binding to an unidentified protein receptor is thought to be required (2). Entry (3) and uncoating (4) proceed through as-yet-undefined pathways. (5) The incoming viral genome is translated, through interactions with VPg at the 5′ end of the genome (red triangle) and the cellular translation machinery. (6) The ORF1 polyprotein is co- and post-translationally cleaved by the viral protease NS6. (7) The replication complex is formed by recruitment of cellular membranes to the perinuclear region of the cell (not shown), through interactions in part with NS1/2 and NS4. (8) Genome replication occurs via a negative-strand intermediate, and genomic and subgenomic RNA are generated by the viral RdRp (NS7), using both *de novo* and VPg-dependent mechanisms of RNA synthesis. (9) The replicated genomes are translated (within the replication complex) or packaged into the capsid, VP1, for virion assembly and exit (10). *(Adapted from Thorne L.G., Goodfellow I.G. Norovirus gene expression and replication.* J Gen Virol *2014; 95(Pt 2):278-91.)*

Clinical Manifestations

The usual clinical characteristics of norovirus and sapovirus infections are presented in Table 162-3. Most of the time, infections are acute, short-lived or asymptomatic. Nevertheless, severe or prolonged illness and death may occur. Severe outcomes have been associated with the GII.4 NoV strains. Populations at risk include the elderly in healthcare facilities, young infants, and immunosuppressed individuals. Chronic debilitating conditions are usually present. Immediate causes of death include: aspiration pneumonia, sepsis, gastrointestinal bleeding, perforation or necrotizing enterocolitis.[96]

Diagnostic Microbiology

The preferred method for NoV and SaV detection is real-time reverse transcription-PCR (RT-PCR). It is very sensitive (10–100 virions) and can be used for clinical and environmental specimens. It is also used to quantify viral load (RT-qPCR). RT-PCR is used for genotyping by Centers of Disease Control and Prevention (CDC) surveillance of NoV outbreaks.

Enzyme immunoassays (EIAs) are rapid and useful for testing multiple specimens during outbreaks; however, their sensitivity is about 50% and negative samples should be retested by RT-PCR. EIAs should not replace RT-PCR during outbreak investigations.

EIAs have been very useful for the detection of antibodies to the viruses in sero-epidemiological studies.[97]

Whole diarrhea stools should be collected within 48–72 hours of illness. If testing is done within 3 weeks, the sample should be kept refrigerated at 39°F (4°C); for longer times, samples should be frozen at −4°F (−20°C). For shipping, each sample should be sealed in a separate plastic bag and kept on frozen refrigerant packs in an insulated, waterproof, polystyrene container. Vomitus samples should be processed in the same way as stools. Water and environmental samples, and food and shellfish samples, should be processed under CDC and FDA guidance respectively.[98]

Enteric Adenoviruses

Enteric adenoviruses were first described in 1975.[99] The family Adenoviridae includes 57 human adenoviruses classified into seven groups (A–G). Most are respiratory adenoviruses but two, serotypes 40 and 41 that belong to group F, are enteric pathogens. Group D adenoviruses may also be enteropathogenic in some populations.[100]

Adenoviruses are non-enveloped viruses with a dsDNA genome surrounded by an icosahedral capsid with fiber-like projections from each of the 12 vertices (Table 162-1). Each virion contains 240 hexons (the major surface protein) and 12 pentons. Each penton consists of a base and a fiber. Genus-specific antigens are located in the hexon. Type-specific antigens are located in the hexon and the fiber and elicit serum-neutralizing antibodies. The fiber protein of most adenoviruses binds to the coxsackie–adenovirus receptor (CAR) of epithelial cells. The penton base mediates internalization of the virus. Infected cells degenerate in a process dependent on the E3 virus protein.[101] The mechanism(s) by which serotypes 40 and 41 induce gastroenteritis remains unclear.

Enteric adenoviruses have worldwide distribution, mainly affecting young children, and are responsible for 4% of acute gastroenteritis episodes seen in outpatient clinics and 2–22% seen in hospitalized children.[102] Outbreaks lasting 7–44 days have occurred in hospitals and daycare centers with approximately 40% of children infected, half of them asymptomatically.[103] Transmission is person-to-person by the fecal–oral route. Infected persons develop group- and type-specific antibodies that confer long-term immunity. Stool excretion of adenoviruses lasts 10–14 days, from 2 days before to 5 days after end of diarrhea. Asymptomatic excretion may last months to years; thus, their isolation in diarrheic stools does not necessarily mean acute infection. Adenoviruses are less resistant than RVs and are rapidly inactivated at 133°F (56°C) and by exposure to ultraviolet light or formalin. Viral antigen detection in stool by immunoassay is the diagnostic test of choice, sensitivity and specificity are 98% when compared with EM. Real-time RT-PCR has proven superior to immunoassays and EM.[104] PCR amplification can be used for serotype determination. Serological tests are rarely used but specific antibodies can be detected by neutralization or hemagglutination inhibition assays. Enteric adenoviruses are difficult to grow in routine cell lines (e.g. Intestine 407, HEK293 and others), but isolation methods are improving.[105] The clinical manifestations of enteric adenoviruses are presented in Table 162-3. In general, the disease is milder but more prolonged than that with RV. Treatment is supportive. Cidofovir (or its oral lipid conjugate brincidofovir) alone or with ribavirin have been used for immunocompromised patients.

Astroviruses

Astroviruses belong to the family Astroviridae. They were first described in 1975 as small (28 nm) particles with a five- or six-pointed star appearance on EM.[106] Later studies showed an icosahedral, 41 nm morphology with well-defined spikes (Figure 162-4). Subjected to high pH, they transform to the previously described star.[106] The virus is non-enveloped, with a single-stranded, positive-sense RNA genome that contains three ORFs. ORF1a and ORF1b encode the viral protease and polymerase, respectively. ORF2 encodes a protein capsid precursor, which gives rise to VP32, VP29 and VP26 (structural capsid proteins). VP26 and VP29 appear to be responsible for antigenic variation.[107] Eight serotypes have been described (HAstV-1 to HAstV-8). Astroviruses infect mammals and birds and some transmission may be zoonotic.[108] Human astroviruses are responsible for 2–4% of endemic diarrhea in children worldwide; HAstV-1 is the most prevalent.[109,110] They have been associated with outbreaks in daycare centers, schools and pediatric wards. Infection confers protective antibodies, which increase with age (>80% of adults have antibodies). Immunocompromised subjects and the elderly may also be affected.[111]

Histopathologic studies show infection of mature epithelial cells of the small intestine,[112] without inflammatory response. The virus is inactivated by methanol 70–90% and heating at 140°F (60°C) for 10 minutes; however, it is resistant to chloroform and ethanol. Diagnosis can be made by commercial immunoassays with good sensitivity and specificity when compared with EM and RT-PCR.[110] Astroviruses can be grown in Caco-2 cells. The clinical characteristics of astrovirus infection are presented in Table 162-3. Symptoms are similar to those of RV infection but less severe. Management is supportive.

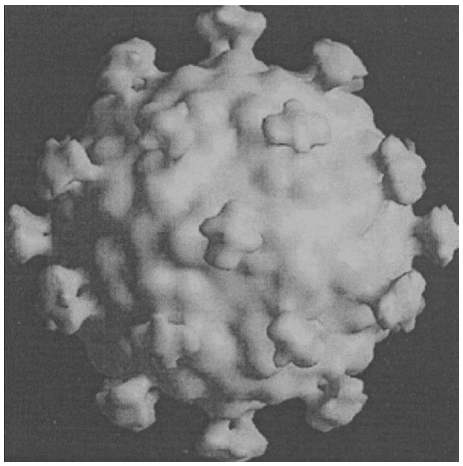


Figure 162-4 Three-dimensional reconstruction of cryoelectron microscopy image of human astrovirus. *(Reproduced with permission from Mendez E., Arias C. Astroviruses. In: Knipe D.M.* et al., *eds.* Field's virology. *5th ed. Philadelphia: Lippincott Williams and Wilkins 2007: 981-1000.)*

Other Viruses

Cases of human gastroenteritis have been associated with parechoviruses, enteroviruses, cardioviruses, kuboviruses, coronaviruses, toroviruses, pestiviruses; parvoviruses, picobirnaviruses; and others, but their role as agents of gastroenteritis is under study.

Management

Most viral gastroenteritis cases are of mild to moderate severity and self-limited. Severe illness occurs mainly in young children, the elderly and immunocompromised patients. No specific antivirals exist for any of the gastroenteritis viruses.

Primary objectives of management are prevention and treatment of dehydration and malnutrition. Most patients can be treated at home with oral rehydration solutions (ORS) and feeding with their regular diet.[113] ORS may prevent 93% of diarrheal deaths.[114] Occasionally, hospitalization and intravenous fluids may be needed for severe illness.

Although lactose malabsorption develops frequently during acute gastroenteritis, most children can be fed lactose-containing formulas in small frequent feeds. Human milk, despite its high lactose content, reduces stool output and provides excellent nutrients and anti-infectious factors; therefore, breast-feeding should be continued. The protective effects of breast-feeding on diarrhea morbidity and mortality have been confirmed.[115]

A specially formulated ORS (ReSoMal) with less sodium, more potassium and glucose and the addition of magnesium, copper and zinc, as well as continuous feeding with calorie-dense foods, are recommended for malnourished patients.[116] The Ready-to-Use Therapeutic Foods have been proven successful.[117]

In LMIC, vitamin A supplementation reduces all-cause diarrhea mortality by 30% in children aged 6–59 months; and zinc, given for 10–14 days during and after a diarrheal episode, decreases diarrhea mortality by 23%.[118,119]

Antiemetics are usually unnecessary; single dose ondansetron can reduce vomiting, use of intravenous fluids and length of stay[120] but its routine use is not supported by the CDC.[121] Adsorbents (kaolin, pectin) and antimotility agents (opiates, loperamide) do not affect the diarrhea mechanisms and may have serious side effects such as paralytic ileus.

Nitazoxanide, bismuth subsalicylate, probiotics, bovine colostrum and human serum immunoglobulin have been tried in patients with severe illness with modest effect. Development of specific antivirals is still in a very early stage.[122]

Prevention

Hygienic measures decrease person-to-person spread; however, these measures are difficult to enforce in situations involving crowding, young children, nursing homes, etc. Some viruses may survive in the environment for weeks and are resistant to commonly used disinfectants, so transmission of the disease continues even in places with good sanitation. Outbreaks require furloughing ill personnel, thoroughly cooking food, disinfecting the environment and properly handling food, water and sanitation. Careful hand washing cannot be overemphasized, especially among food handlers and personnel from hospitals, schools and daycare centers. Hospitalized or other institutionalized patients should be placed under universal precautions with added contact isolation until 48–72 hours after symptoms resolution.[123]

Chemical disinfectants can interrupt virus spread from the environment. Special attention should be given to bathrooms, door knobs, hand rails and food preparation surfaces. Commonly used disinfectants are 70% ethanol, 6% hydrogen peroxide, 2500 ppm chlorine, povidone–iodine, ultraviolet radiation and heat. Since fecal matter inactivates the hypochlorites, it should be removed before application. Household laundry can be washed with detergent and bleach, followed by a drying cycle. Heat (176°F (80°C)) for at least 1 minute or high pressure processing have also been used.[124]

Breast-feeding may reduce the severity and duration of RV illness, but not the incidence,[36] and depending on the population being studied,[125,126] artificial formulas supplemented with probiotics may reduce the incidence of diarrhea and shorten RV shedding.[127] The most practical and effective intervention to prevent gastroenteritis is vaccination. However, such vaccines are available only for rotavirus.

TABLE 162-6 Comparison of Two Licensed Rotavirus Vaccines

Name	RotaTeq®	Rotarix®
Producer	Merck & Co., Inc.	GlaxoSmithKline
Vaccine type	Live, bovine–human reassortant	Live-attenuated human RV strain (RIX4414)
Serotypes	Pentavalent: G1, G2, G3, G4, P1[8]	Monovalent: G1P[8]
Dose	>2 × 10^6 infective doses, each	>1 × 10^6 infective doses
Administration	Oral, three doses at 2, 4 and 6 months of age	Oral, two doses at 2 and 4 months of age
Intussusception risk*	~1/100 000	~5/100 000
Efficacy:†		
RV GE, any severity	74 (67–80)	73 (27–91)
RV GE, severe	98 (88–100)	85 (72–92)
All diarrhea hospitalization	59 (52–65)	42 (29–53)
Virus shedding	9%	50–80%

GE, gastroenteritis; RV, rotavirus.
*Odds ratio vaccine vs placebo (95% CI).
†Percent decrease vaccine vs placebo (95% CI).

The first commercial RV vaccine, RotaShield® (Wyeth-Ayerst Laboratories), was licensed in the USA in 1998. The vaccine was 49% effective in preventing all RV diarrheas and 80% effective in preventing severe RV diarrhea,[128] but it was suspended due to an association with intussusception, estimated as one additional case/10 000 vaccinated infants.[129] A decade later, two new RV vaccines were licensed. RotaTeq® (or RV5), a live vaccine (Table 162-6) containing five bovine–human reassortant strains, four expressing human G1–G4 with bovine P7[5] specificity, and one expressing bovine G6 with human P1[8]. Three doses administered at 2, 4 and 6 months of age demonstrated 74% efficacy to prevent any RV disease and 98% of severe disease.[130] A second RV vaccine, Rotarix® (or RV1) is a live monovalent vaccine (Table 162-6) derived of a human attenuated strain 89–12 of G1P[8] specificity. Two doses at 2 and 4 months proved effective in preventing any (73%) or severe (85%) RV disease.[131] The World Health Organization recommended inclusion of RV vaccines into national immunization programs in the Americas and Europe in 2007 and worldwide in 2009.[132]

In the USA, RV5 was introduced in 2006 and RV1 in 2008, resulting in >80% reduction in RV-related hospitalization, emergency department (ED) visits and outpatient visits. Concomitantly, there was ~50% decrease in all-cause gastroenteritis visits and hospitalizations. The benefit has been noted even with single dose of either vaccine and has included heterotypic protection.[133] Herd immunity is also present with either vaccine.[134] Countries that introduced RV vaccines have seen a virtual disappearance of the previously predominant G1P[8] strains and a proportional increase of other genotypes, especially G3P[8] (mainly seen in those using RV5) and G2P[4] (mainly in those using RV1).[135-137] Whether the change represents an effect of vaccine pressure or rather secular changes in circulating RV strains is unclear.

Studies in LMIC in Africa[138] and Asia[139] showed lower efficacy of RV5 and RV1 with prevention of severe disease varying between 39% and 77%.[140]

Post-licensure surveillance has detected risk of intussusception for RV5 and RV1, mainly after the first dose and estimated at 1–5 additional cases/100 000 infants vaccinated.[141,142] This risk is considered small and is outweighed by the benefits of vaccination.[143]

Some countries are pursuing their own RV vaccines but few have advanced through clinical testing. The Lanzhou Lamb RV (LLR) vaccine has been licensed in China since 2000 with reported effectiveness of 73% and 44% for RV-hospitalizations and all RV diarrhea respectively.[144,145] In India, a vaccine is being developed based on a natural human-bovine RV reassortant (116E) with 54% efficacy to prevent severe RV disease.[146] Few other candidate vaccines have entered early phase clinical trials.

No licensed vaccine exists against norovirus. Vaccine development has been complicated by several factors including: multiple virus types; antigenic variation; inability to culture the virus; no small animal model; partial understanding of immunity; and effect of previous infections. NoV VLPs given orally to mice and human volunteers are safe and induce IgG1 and IgA antibody responses[147] and a NoV VLP vaccine given intranasally to volunteers reduced the frequency of gastroenteritis and subclinical infections when the participants were given the Norwalk virus.[148]

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