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# Sapovirus: an emerging cause of childhood diarrhea

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## Abstract

**Purpose of review:** *Sapovirus*, a genus in the *Caliciviridae* family alongside norovirus, is increasingly recognized as an important cause of childhood diarrhea. Some challenges exist in our ability to better understand sapovirus infections, including the inability to grow sapovirus in cell culture, which has hindered diagnosis and studies of immunity. Another challenge is that individuals with sapovirus infection are commonly co-infected with other enteric pathogens, complicating our ability to attribute the diarrhea episode to a single pathogen.

**Recent findings:** Development of molecular methods for sapovirus detection has increased our ability to measure disease prevalence. The prevalence of sapovirus varies between 1 to 17% of diarrhea episodes worldwide, with the highest burden in young children and older adults. Further, epidemiological studies have used novel approaches to account for the presence of co-infections with other enteric pathogens; one multi-site cohort study of children under two years of age found that sapovirus had the second highest attributable incidence among all diarrheal pathogens studied.

**Summary:** Especially in settings where rotavirus vaccines have been introduced, efforts to reduce the overall burden of childhood diarrhea should focus on the reduction of sapovirus transmission and disease burden.

### Keywords

Sapovirus; diarrhea; gastroenteritis; childhood; Caliciviridae

## Introduction

Sapoviruses form a genus in the *Caliciviridae* family, a family which also includes noroviruses. The burden of sapovirus disease went underestimated for several decades after its discovery due to the lack of diagnostic tests for sapovirus detection other than electron microscopy. With the development and increasing use of molecular diagnostic tests, there is growing evidence of the importance of sapovirus to the global burden of childhood diarrhea.

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There are no conflicts of interest.

Most notably in countries where rotavirus vaccines have been introduced, sapovirus is among the leading contributors to diarrhea in young children.(1,2) Sapovirus has also been identified as an important cause of diarrhea in older adults, especially those living in long-term care facilities(3), and in individuals with immunocompromising conditions.(4,5) An extensive review of sapovirus was published by Oka, et al, in 2015.(6) This review includes a concise update of the literature on sapovirus since that review.

## Text of review

### SAPOVIRUS CLASSIFICATION

Sapoviruses were named after an outbreak of diarrhea in children in Sapporo, Japan; (7,8) similar viruses were observed in other countries (Manchester UK 1993 (GI.1), Parkville USA 1997 (GI.2), Bristol UK 1998 (GII.1) and Mex340 (GII.2)).(9–11) Nucleotide sequencing, capsid cloning, and virus-like particles (VLP) synthesis of these Sapporo-like caliciviruses showed genetic and antigenic differences from other *Caliciviridae* (12–14), and *Sapovirus* was recognized as a separate genus. (10,15–17) Sapoviruses have been detected in several mammals, including swine, sea lions, dogs, bats, and rats(6), but spillover of animal sapoviruses to humans has not been reported, suggesting host restriction. Overall, 19 sapovirus genogroups (GI - GXIX) have been described, with genogroups GI, GII, GIV and GV limited to humans. A total of 19 genetic variants within genogroups, denominated genotypes, have been described in humans (GI.1–7; GII.1–8; GIV.1 and GV.1–2).

### DIAGNOSIS OF SAPOVIRUS

Reverse transcription (RT)-PCR is the most common method of sapovirus diagnosis. However, diagnosis of sapovirus is typically not performed due to the cost and lack of access to PCR in most of the world. Also, detection of sapovirus does not usually change clinical management. However, there are a growing number of multiplex clinical diagnostic tests that include sapovirus.(18) Another challenge is that primers used for sapovirus detection were designed from limited numbers of nucleotides sequences available in the GenBank, thus, current circulating strains might not be efficiently detected.(19) Several efforts have been made to increase the number of full genome sequences (20–22) and develop broadly reactive primers which may be more sensitive.(23) Sapovirus genotyping is often performed for epidemiological studies. Genotyping is more successful for samples with higher viral loads (cycle threshold < 30) (24); the association between viral loads and clinical symptoms remains to be explored.

Due to the limitations of current molecular methods, outbreaks caused by sapovirus may be underestimated. For instance, electron microscopy of stools and whole genome sequencing was required for the identification of sapovirus in a food-borne outbreak in Sweden, because the RT-PCR used for screening was unable to detect this new variant, GV.2.(25,26) The identification of sapovirus as a cause of foodborne or waterborne outbreaks is limited and requires an improvement in molecular methods used for screening.

## BURDEN OF DISEASE

Sapoviruses are responsible for both sporadic cases and outbreaks of acute diarrhea. Sapovirus outbreaks have mainly been reported in high-income countries, including in day care centers,(27,28) schools,(27,29,30) a military institution,(31) hospitals,(32,33) and nursing homes.(3,27,34,35) The detection frequency of sapovirus is variable across geographic locations and age groups, but has been reported to be associated with 1% to 17% of diarrhea cases in different settings (Table 1).

Sapovirus was detected in 10% of US children <18 years of age receiving care for diarrhea in both the inpatient and outpatient settings(2), 8% of South African children <5 years of age hospitalized for diarrhea,(36) and 12–19% of young children with diarrhea in Central American cohorts.(37,38) In general, studies limited to children, conducted in LMICs, focused on studying sapovirus, and performed in recent years show higher detection of sapovirus. It is possible that increased detection in recent years may be due to improvements in molecular detection, including the use of more specific primers(23), and the roll-out of rotavirus vaccines, which increases the proportion of remaining diarrhea cases in which sapovirus is detected. Finally, most but not all studies that include healthy controls show lower sapovirus detection in stools from asymptomatic as compared to symptomatic individuals.(1,2,37–41)

One factor that complicates our understanding of the burden of sapovirus disease is the common finding of co-infections with multiple enteric pathogens, especially in LMIC settings.(1,42,43) The multi-site Malnutrition and Enteric Disease (MAL-ED) study addressed this problem by estimating the attributable burden of each enteric pathogen by accounting for detection in healthy control children. Using this approach, MAL-ED reported sapovirus to have the third highest attributable incidence for diarrhea among children under 12 months of age, and the second highest attributable incidence among children between 12 and 24 months of age.(1) Further, in the three MAL-ED research sites where rotavirus vaccines had been introduced, the attributable incidence of sapovirus had a higher point estimate than rotavirus. However, unlike several other enteric pathogens, sapovirus diarrhea was not associated with delays in linear growth in children.(44)

## BREATH AND DISTRIBUTION OF SAPOVIRUS GENOTYPES

Understanding genotype distribution provides insights into patterns of transmission, appropriate diagnosis of circulating strains, immunity in populations, and future vaccine development. GI.1 remains the most common genotype across age groups and recruitment settings, followed by GII.1, GII.2 and GI.1.(24,72) In surveillance studies of children with sapovirus diarrhea, the frequency of genotype GI.1 can range from 10% to 63%, with GI.2 and GII.1 the second most commonly reported genotypes. A hospital-based study showed fluctuation of genotypes between sampling years and geographic areas.(77) Varela and coworkers observed that the dominant genotypes, GI.1, GI.2 and GII.2, were more frequently detected in the first year of life but also in older adults.(24) It is possible that infection from these common sapovirus genotypes early in life may induce natural protection that wanes later in life. Another interesting trend is that studies reporting high frequencies of GI.1 usually report low frequencies of GI.2 and GII.1; and likewise, studies

with high frequencies of GI.2 and GII.1 report lower frequencies of GI.1(60,62,78) (Fig. 1). GII.3, GII.4 and GII.5 have been reported at high frequencies in some studies and have been described as emerging genotypes.(48,61,79) In asymptomatic subjects, the distribution of genotypes is similar to that observed in symptomatic subjects with GI.1 ranging from 18% to 75%, followed by GI.2, GII.1 and GII.2.(73,78,81,82) The most common genogroups observed in outbreaks are GI and GIV.(83)Finally, unlike norovirus, which evolves to cause periodic global outbreaks from genetic variants, sapovirus showed limited intra-genotype diversity over a forty year period.(80)

Sapovirus genotype diversity may have implications for the development of broadly protective sapovirus vaccines. However, more studies are needed to understand the relationship between genotypes and antigenic types, as is it not currently known whether the immune response to natural sapovirus infections are genotype- or genogroup-specific or cross-reactive. One important challenge for these studies is the absence of cell culture systems for antigen production and for viral neutralization studies which could inform the appropriate vaccine design.

## CHALLENGES TO STUDYING SAPOVIRUS

Human sapovirus cannot be adapted and propagated in the most efficient cell culture systems currently available and no animal model is available.(84) Such limitations preclude efforts to better understand the replication cycle and pathogenesis, and deter vaccine development and the search for agents that limit viral replication. Moreover, studies to understand the breath of the immune response are also challenging. An important advance was the transformation of cloned capsid genes from sapovirus into insect cells, which then assembles into VLPs providing opportunities to study antigenicity among genogroups and genotypes; however, expression levels are low, making it difficult to use these approaches in large studies. (85–87) The lack of efficient cell culture also limits the production of reagents (antigens and monoclonal antibodies) for rapid diagnostic tests. The observation that human norovirus, another difficult to culture calicivirus, was able to replicate in stem cell-derived human enteroids (88), suggests that sapovirus propagation may be possible in this system.

## TRANSMISSION AND RISK FACTORS FOR SAPOVIRUS DIARRHEA

Sapovirus is thought to spread person-to-person,(89) through wastewater intrusion of drinking water sources,(90) and in contaminated food.(26,91,92) Household crowding(36) and having recent contact with individuals with gastrointestinal symptoms have been identified as risk factors for sapovirus diarrhea.(89) Among food-borne transmissions, shellfish are a recognized source of sapovirus infections.(93–95)

Sapovirus was reported to shed in the stool for a median of 18.5 days in children, with no difference in shedding duration between symptomatic and asymptomatic infections.(82) Children infected with sapovirus can shed approximately 1 million genome copies of sapovirus per gram of stool (range: $2 \times 10^3$ and $7 \times 10^{11}$).(24,96,97) A study of children in Danish day cares found that 21% of all children shed sapovirus, suggesting that day cares may act as year-round reservoirs for sapovirus transmission.(39)

Age is a clear risk factor for sapovirus diarrhea: children under age 5 are at highest risk, followed by older adults.(98) Sapovirus caused 13% of gastroenteritis outbreaks in nursing homes studied in England.(3) A study of outpatients with diarrhea in Spain found that sapovirus detection followed a U-shaped curve: highest in children aged 0–2 years, decreasing in older children and young adults, and then increasing in adults > 60 years of age.(24) Among children, the incidence is greatest in the second year of life,(36) once maternal immunity wanes and the child is increasingly exposed to contamination of food or the environment. A birth cohort study in Peru found the incidence of sapovirus infection in the first and second years of life was 4.3 and 11.1 per 100 child-months, respectively. By age 2 years, 82% of children had experienced at least one sapovirus infection, and 64% had experienced at least one sapovirus diarrhea episode.(82) Unlike norovirus infection, sapovirus infection does not appear to be associated with host histo-blood group antigen expression.(101,102) Finally, it is not known if contact with animals is a risk factor for sapovirus; the zoonotic potential of sapovirus needs further investigation.(99,100)

Sapovirus diarrhea can occur throughout the year, however, it was most frequently found in June and July in Japan.(62) In Spain, detection peaked during autumn and early spring,(24) while in the Netherlands, sapovirus was most commonly detected in the winter and spring. (58) In Nicaragua, sapovirus was most frequently detected early during the rainy season, and in a Peruvian birth cohort, sapovirus risk increased following La Niña-associated flooding. (101)

## CLINICAL SYMPTOMS

Clinical symptoms of sapovirus infection are similar to other intestinal viruses. Common symptoms of sapovirus infection include diarrhea, nausea, vomiting, and abdominal pain which usually resolve within one week.(6,40,102) A birth cohort in Peru reported that 40% of children with sapovirus diarrhea experienced vomiting and 10% experienced fever.(40) As compared to norovirus episodes, sapovirus episodes had less vomiting,(102,103) and as compared to rotavirus episodes, sapovirus episodes had less fever.(103)

While earlier studies suggested that sapovirus resulted in milder symptoms as compared to diarrhea from other causes(103,104), more recent studies show that sapovirus is similar in severity to other etiologies(37,105) and is also detected in hospitalized children, (48,64,69,105) ranging from 15%(48) of children hospitalized for diarrhea in Nicaragua to 4% in a US-based study.(64) A hospital-based study in South Africa identified sapovirus in 11% of child deaths due to diarrhea.(36) Finally, while primarily associated with acute diarrhea, sapovirus has also been detected in cases of chronic diarrhea, particularly in individuals with immunocompromising conditions.(4,5)

## DEVELOPMENT OF IMMUNITY

Humoral immunity to sapovirus has been demonstrated in acute and convalescent samples using purified viruses from infected stool samples.(7) Further, seroprevalence studies conducted in the years after sapovirus had been identified showed rising seroprevalence with age, reaching a high level in older children that continues into adulthood.(106) As the intestinal mucosa is the location of infection, it is presumed that IgA antibodies are

important to immune protection and that innate immune activation is mediated through the interferon pathway.(107) Chronic sapovirus infections in individuals with immune deficiencies or those taking immunosuppressant medications show that clearance of infections is dependent on intact host immune responses.(4,108) There is little known about the breath of immunity following a sapovirus infection. Studies using hyperimmune sera show strong reactivity against VLPs of homologous sapoviruses, but little cross reactivity between genogroups, suggesting that human sapovirus genogroups are antigenically distinct.(17)

Observational field studies show that sapovirus diarrhea is more common in young children as compared to older children and adults, suggesting that early life infections provide immunity.(102,109) A Peruvian birth cohort found that repeat sapovirus infections do occur, but repeat infections with same genotype are rare: over two years of surveillance; 59/82 children who experienced a sapovirus infection went on to have a repeat sapovirus infection, however only three repeat infections were of the same genotype.(82) Taken as a whole, these data suggest that first sapovirus infections provide immunity against homologous infections, but little protection against infections of different genogroups. Further, the low incidence of symptomatic sapovirus episodes in the first months of life suggests early protection from maternal immunity.

A recent study by Rogawski, et al,(110) examined the protective efficacy of first enteric infections on subsequent infections in MAL-ED; they found that a first sapovirus infection provided modest protection against subsequent infections [adjusted Hazard Ratio of 0.78, 95% confidence interval (0.69, 0.88)]. Now that more tools to study sapovirus immunity are becoming available, research is needed to understand the bredth of immunity following infection and to identify protective epitopes. This knowledge would improve our understanding of the development of natural immunity and guide future vaccine development.

## TREATMENTS

There are no specific therapeutics agents or vaccines for sapovirus diarrhea. Currently, the World Health Organization recommends treating diarrhea with oral rehydration solution, usual nutrition or continued breastfeeding, and zinc supplementation (in LMIC).(111) Anti-motility agents, such as loperamide, should be avoided in children <18 years, however, while not FDA-approved, the Infectious Diseases Society of America includes the anti-nausea medicine, ondansetron, as an option for individuals >4 years of age with diarrhea to support oral rehydration.(112) Rapid intravenous hydration should be provided to individuals with severe dehydration resulting from diarrhea.(111)

## PREVENTION OF SAPOVIRUS INFECTION

While there is little known specifically about the environmental decontamination of sapoviruses, measures used to control norovirus are also likely effective against sapovirus, such as frequent hand washing, proper disposal of fecal- or vomit-soiled materials, limiting contact with infected individuals, and environmental disinfection with chlorine-containing cleaning agents.(113,114) As for norovirus, the safe handling of food would likely decrease

food-borne transmission of sapovirus. While improving water quantity and quality is likely to contribute to decrease sapovirus transmission, the high burden of sapovirus in both high- and low-income settings argues against the potential that improvements in water sources alone will eliminate sapovirus burden. There is little known about the potential for breastfeeding to protect against sapovirus diarrhea in infants and no licensed vaccines against sapoviruses are available.

## Conclusion

With increasing molecular detection, sapovirus is now recognized as an important cause of diarrhea, primarily in young children. As there are no vaccines currently available against sapovirus, prevention includes hygiene, safe food handling, and improved water sources. More research is needed to better understand transmission patterns and risk factors for sapovirus infection to guide prevention efforts. Treatment of sapovirus diarrhea episodes is similar to diarrhea due to other causes and includes the use of oral rehydration. Limited immunological and epidemiological data suggest that children develop natural immunity to sapovirus, providing optimism for the potential success of future sapovirus vaccines.

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**Key points**

- With the increasing use of molecular methods of detection, sapovirus is now recognized as an important cause of diarrhea in children and older adults worldwide.
- The severity of illness of sapovirus infections is similar to that of other intestinal viruses; sapovirus can also cause chronic diarrhea, particularly in individuals with immunocompromising conditions.
- Observational studies suggest that sapovirus infections during early childhood confer immunity and repeat infections with the same sapovirus genotype are rare.
- Sapovirus can spread person-to-person, and through contaminated drinking water and food; day care centers may serve as year-round reservoirs of sapovirus transmission.

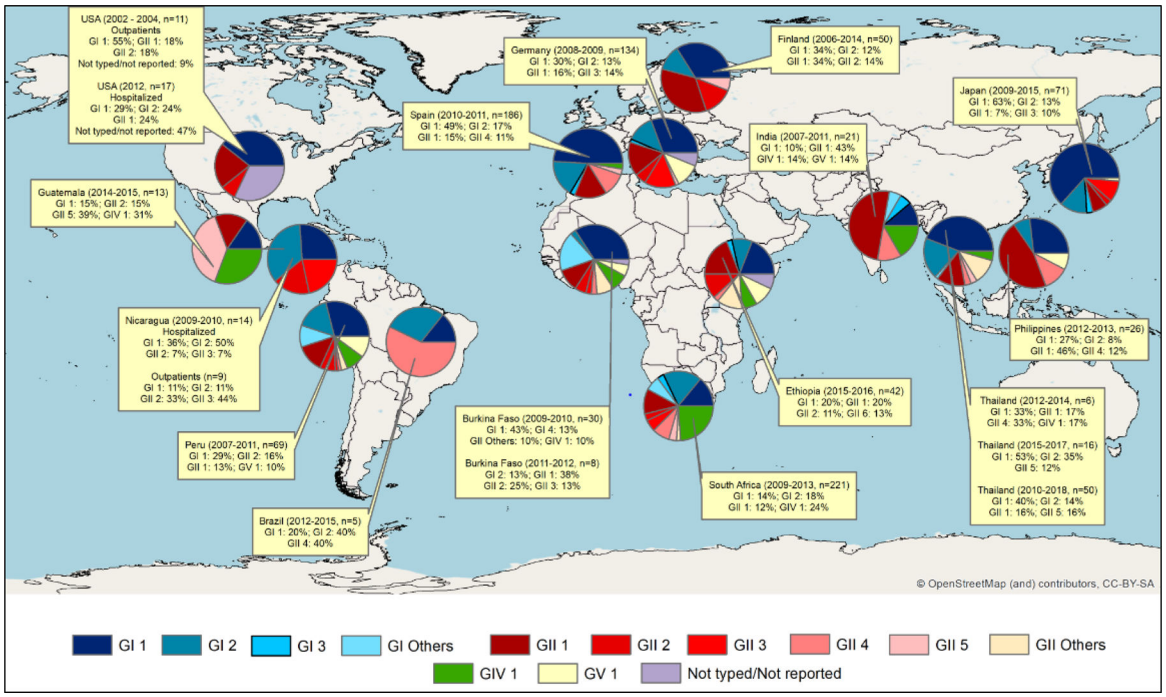


**Figure 1.**

Sapovirus genotypes reported in surveillance studies lasting at least one year and using RT-PCR for sapovirus detection in diarrheic stools in the last decade.

In these studies, genotypes were assigned according to phylogenetic analysis of partial capsid gene, with some exceptions that used near full genomes. ArcGis 10.7 was used to display sapovirus distribution by country and study. The basic map was provided by OpenStreetMap.

**Table 1.**

Sapovirus detection proportion in diarrhea cases or sapovirus diarrhea incidence from studies that involved more than 300 participants during the period 2014–2020

| Publication Year | Setting | Country | Study Design | Time Frame | Number of Subjects | Age | Detection Proportion by PCR | Reference |
|---|---|---|---|---|---|---|---|---|
| 2014 | Inpatients | Thailand | Prospective, facility-based | January to December 2007, 2010 to 2011 | 567 | < 5 years | 1.2% | (45) |
| 2014 | Outpatients | China | Prospective, facility-based | January to December 2011 | 1110 | ≤60 years | 1.5% | (46) |
| 2014 | Inpatients or outpatients | China | Prospective, facility-based | January 2006 to December 2011 | 334 | < 5 years | 0.60% | (47) |
| 2014 | Community | Nicaragua | Prospective, community-based cohort | January 2010 to January 2011 | 826 | <5 years | 17%; Incidence: 19 per 100 child-years | (38) |
| 2014 | Inpatients, outpatients, and community | Nicaragua | Prospective, facility-based | September 2009 to October 2010 | 330 | ≤ 5 years | 17% | (48) |
| 2015 | Outpatients | Japan | Retrospective, facility-based | 2010 to 2012 | 751 | <15 years | 4.8% | (49) |
| 2015 | Inpatients and outpatients | China | Prospective, facility-based | July 2010 to December 2012 | 1128 | <14 years | 1.2% | (50) |
| 2015 | Outpatients | China | Prospective, facility-based | January 2010 to December 2011 | 436 | ≤5 years | 0.46% | (51) |
| 2015 | Outpatients | China | Prospective, facility-based | April 2011 to March 2013 | 3832 | All ages | 8.3% | (52) |
| 2016 | Inpatients | South Africa | Prospective, facility-based | 2009 to 2013 | 3103 | <5 years | 7.7% | (36) |
| 2016 | Inpatient and emergency department visits | Canada | Prospective, facility-based | February 2012 to May 2014 | 734 | 8 weeks to < 3 years | 6.4% | (53) |
| 2016 | Community | Peru | Prospective, community-based cohort | 2009 to 2010 | 300 diarrheal stools | <2 years | 12% | (54) |
| 2016 | Outpatients | USA | Prospective, facility-based | August 2012 to September 2013 | 1099 | All ages | 2%; Incidence: 1.6 per 100 person-years | (55) |
| 2016 | Outpatients | Japan | Retrospective, facility-based | September 2008 to August 2014 | 1871 | 2 weeks - 84 years | 3.6% | (56) |
| 2016 | Inpatients | China | Prospective, facility-based | May 2011 to January 2013 | 461 | <5 years | 6.5% | (57) |
| 2016 | Outpatients | Dutch | Prospective, day care-based | April 2013 to October 2014 | 981 children | <5 years | 3.8% | (58) |

| Publication Year | Setting | Country | Study Design | Time Frame | Number of Subjects | Age | Detection Proportion by PCR | Reference |
|---|---|---|---|---|---|---|---|---|
| 2016 | Inpatients (children only) and outpatients | Brazil | Prospective, facility-based | January 2012 to December 2014 | 341 | All ages | 3.5% | (59) |
| 2016 | Inpatients and outpatients | Burkina Faso | Prospective, facility-based | November 2011 to September 2012 | 263 with diarrhea; 50 controls | <5 years | 10% | (60) |
| 2017 | Inpatients | Thailand | Prospective, facility-based | January 2012 to December 2014 | 889 | <5 years | 0.7% | (61) |
| 2017 | Not stated | Japan | Retrospective, facility-based | September 2009 to August 2015 | 948 | <15 years | 7.5% | (62) |
| 2017 | Inpatients and outpatients | Burkina Faso | Prospective, facility-based | November 2011 to September 2012 | 443 | All ages (263 <5 years) | 8.8% | (63) |
| 2017 | Inpatients and outpatients | USA | Prospective, facility-based | October 2010 to September 2012 | 1089 | <18 years | 5.9% | (64) |
| 2018 | Inpatients | Russia | Retrospective, facility-based | January 2009 to January 2014 | 469 | <5 years old | 1.4% | (65) |
| 2018 | Community | Multicenter (Brazil, Bangladesh, India, Nepal, Pakistan, Peru, South Africa, Tanzania) | Prospective, community-based cohort | November 2009 to February 2012 | 1715 | <2 years old | Attributable incidence: 22.8 per 100 children-years | (1) |
| 2018 | Inpatients | Italy | Prospective, facility-based | November 2015 to October 2016 | 510 | 2 months to 15 years | 6.0% | (66) |
| 2019 | Inpatients | Thailand | Prospective, facility-based | January 2015 to February 2017 | 843 | 2 months to 15 years | 1.9% | (67) |
| 2019 | Outpatients | Ethiopia | Prospective, facility-based | November 2015 and April 2016 | 450 | <5 years | 10% | (68) |
| 2019 | Inpatients and emergency department visits | Finland | Prospective, facility-based | 2006 to 2014 | 1437 | <16 years | 1.4% before rotavirus vaccine introduction; 5.5% after introduction | (69) |
| 2019 | Outpatients | Spain | Prospective, facility-based | July 2010 to June 2011 | 2667 | All ages | 16% | (24) |
| 2019 | Outpatients | Spain | Retrospective, facility-based | January to April in 2016 and 2017 | 384 | ≤ 5years | 13% among samples testing negative for rotavirus, adenovirus, and enteropathogenic bacteria | (70) |
| 2019 | Inpatients and outpatients | Guatemala | Prospective, facility-based | January 2014 to December 2015 | 471 | <5 years | 7.4% | (71) |

*Curr Opin Infect Dis*. Author manuscript; available in PMC 2021 October 01.

| Publication Year | Setting | Country | Study Design | Time Frame | Number of Subjects | Age | Detection Proportion by PCR | Reference |
|---|---|---|---|---|---|---|---|---|
| 2019 | Inpatients | Germany | Retrospective, facility-based | January 2010 to September 2018 | 5333 | All ages | 1.8% | (4) |
| 2019 | Inpatients | Germany | Prospective and retrospective, facility-based | 2008 to 2009 and 2010 to 2018 | 5897 | <5 years (2008 to 2009) and all ages (2010 to 2018) | 2.4% | (72) |
| 2019 | Inpatients and emergency department visits | USA | Prospective, facility-based | January to December 2012 | 330 cases | <2 years | 3.0% | (73) |
| 2019 | Outpatients | China | Prospective, facility-based | January 2010 to December 2014 | 4,548 | All ages | 1.1% | (74) |
| 2020 | Community and inpatients | China | Prospective, facility-based and community-based cohort | October 2011 to December 2013 | 10,056 | <5 years | 9.6%; Incidence: 12.4 and 11.7 per 1000 child-years in Zhengding and Sanjiang, respectively | (75) |
| 2020 | Inpatients | Thailand | Prospective, facility-based | 2010 to 2018 | 3057 | <15 years | 1.6% | (76) |
| 2020 | Inpatients and outpatients | USA | Prospective, facility-based | January 2012 to November 2015 | 3705 cases | 15 days to 17 years | 10% | (2) |