18

Public Health Risks Associated with Norovirus Gastroentritis

AUTHORS DETAIL

Sara Ijaz[1*], Shama Jamel[2], Ammar Faiz[3], Abdullah Alsayeqh[4], Aiman Mushtaq[5], M. Faizan Elahi Bhatti[1], Khushbakht Asad[5]

[1]Department of Epidemiology and Public health, University of Veterinary and Animal Sciences, Lahore, Pakistan
[2]Department of Pathology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[3]Department of Meat science and technology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[4]Department of Veterinary Medicine, College of Agriculture and Veterinary Medicine, Qassim University, Buraidah 51452, Qassim, Saudi Arabia
[5]University of Veterinary and Animal Sciences, Lahore, Pakistan
*Corresponding author: saraijaz0306@gmail.com

Received: Sept 12, 2022 **Accepted: Dec 20, 2022**

INTRODUCTION

Globally, gastroenteritis is a serious public health concern. Norovirus is currently identified as the primary reason for nonbacterial, acute gastroenteritis in individuals and is categorized as an emerging disease.
Four genera are included in the family Calciviridae, which were given names based on disease characteristics. The two genera were named after vesicular lesions (Vesivirus and Lagovirus), while the other two genera were named after the infected hosts and the location of the first isolation of these species (Sapporo, Japan—Sapovirus; Norwalk, USA—Norovirus), (Cheetham et al. 2006).
The viruses of this family are microscopic and non-enveloped, with an approximate diameter ranging from 27-35 nm. Norovirus is a single-stranded positive-sense RNA virus. They infect a wide range of hosts, including humans, pigs, cattle, dogs, and mink. They can cause a wide range of diseases and lesions in humans, such as digestive tract infections in human beings and animals like pigs, cattle, dogs, and mink etc. Pigs, sea lions, and other marine mammal species could be infected with vesicular lesions, while reproductive failure, stomatitis, upper respiratory tract infection, and hemorrhagic and systemic diseases occur in cats. The original strain of Nov, known as Norwalk virus (NV), was first identified in 1968 and linked to a human gastroenteritis outbreak in Norwalk, Ohio, which was named Norwalk virus (Nov prototype strain) in 1968 (Caul 1996).
Numerous studies show that BoNoVs are frequently found in cattle and occasionally at high frequency in cases of diarrhea in various countries, despite the fact that they have been studied much less than other viruses that are known to be the cause of NCD (neonatal calf diarrhea), such as rotavirus and coronavirus (Castells et al. 2020).
Acute norovirus infection is characterized by nausea, vomiting, diarrhea, stomach cramps, headache, myalgia, and high temperature. Vomiting is frequently projectile and intense (Caul 1996). Norovirus can develop chronic dehydrating diarrhea in immunocompromised patients, which can cause significant consequences and occasional fatality of up to 25% (Frange et al. 2012).

Epidemiology and Prevalence

Both sporadic infections and outbreak cases of acute gastroenteritis are frequently caused by noroviruses. Large epidemics frequently happen in public places like hospitals, nursing homes for the elderly and daycare centers (Matthews et al. 2012).
Noroviruses can be divided into five genogroups based on their considerable genomic diversity. There are at least 30 distinct genotypes that are further divided into three pathogenic genogroups (GI, GII, and GIV) of humans. Drift variations of genotype II have been responsible for many global epidemics (Siebenga et al. 2009).
National surveillance data of norovirus gastroenteritis in Germany are accessible in an electronic database at the Robert Koch Institute, which is the country's public health institute (Jor et al. 2010; Otto et al. 2011). Many epidemiological studies have shown that NoVs are commonly found in humans in addition to those of the bovine, pig and murine species (mice and rats). Few investigations on animal NoV infections have been conducted, and the epidemiology is poorly characterized (Cheetham et al. 2006).
Norovirus is responsible for 60% of cases of acute gastroenteritis in the country, or around 21 million episodes, across the year, as it is stated, by The United States' Centers for Disease Control and Prevention (CDC). Norovirus has also been involved in sporadic disease as an outcome of the inclusion of molecular techniques. Norovirus detection by Reverse transcriptase PCR (RT-PCR) conferred 5 to 31% of reports of gastroenteritis in hospitalized patients and an additional 5 to 36% of reports in patients seeking outpatient assessment (Patel et al. 2008).

Citation: Ijaz S, Jamel S, Faiz A, Alsayeqh A, Mushtaq A, Bhatti MFE, Asad K, 2023. Public Health Risks Associated with Norovirus Gastroentritis. In: Khan A, Abbas RZ, Aguilar-Marcelino L, Saeed NM and Younus M (eds), One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. I, pp: 116-120. https://doi.org/10.47278/book.oht/2023.18

Pathogenesis

The mechanism of disease spread in man and animals is not fully understood. This disease persists for 1-2 days. Acute enteritis with non-hemorrhagic diarrhea, vomiting, lack of appetite, gut ache, and slightly high body temperature are symptoms of infection. The ailment is self-limiting and lasts only 12-60 hours; however, immune-compromised animals may have chronic diarrhea and shed the virus for months or years (Karst et al. 2015).

The primary target cells for virus duplication are mainly intestinal cells of the anterior part of the intestinal tract, causing malabsorption and diarrhea. The intestinal epithelium seems to be unaffected, but the jejunum has developed specific histo-pathological lesions caused by human Nov infection, such as intestinal villi atrophy, intestinal epithelial cell breakdown, hyperplasia of crypt cells, and vacuolated and mononuclear inflammatory infiltrate in the lamina propria of villi. The shortened microvilli and reduced brush border enzyme activity that happen in acute infection related to the mal-absorption (Karst et al. 2015).

Both diarrheal and non-diarrheic cattle fecal samples contain bovine NoV. Newborn Infected calves exhibit diarrhea after 3-4 days of infection, which lasts for only one day. Diseased calves display a lack of appetite on the fourth and fifth day of infection, non-hemorrhagic inflamed intestine, mal-absorption, and discrete diarrhea at the age of 1-8 years in calves. Heartbeats and rate of breathing were maintained within normal ranges, and the temperature of rectum ranges between 37 and 40°C (Jor et al. 2010; Otto et al. 2011). Degeneration of villous and elongation of crypts in the anterior part of small intestine result from infections with bovine NoV genotypes (Hall et al. 1984; Otto et al. 2011).

Bovine NoV GIII.1 infects all entero-absorptive cells, in contrast to other intestinal viruses like bovine rotavirus and norovirus, which mainly infect the tips and bases of villi. It has been hypothesized that the severe villus degeneration and loss of mature intestinal cells caused by the bovine NoVGIII.1 may shorten the duration of infection because fewer cells are available to become infected. However, experimental studies using the bovine GIII.2 strain demonstrated that calves shed the virus in feces for at least 30 days after giving challenge, irrespective of the fecal condition (diarrheic or not) and the length of clinical manifestations (Jor et al. 2010). Bovine NoV GIII 2 was seen in the calves without showing significant histological changes such as villous atrophy, mortification of intestinal cells, and diarrhea. (Jung et al. 2014).

The importance of porcine NoV is still unclear as a cause of diarrhea in pigs. The porcine NoV incubation period in an experimental challenge of piglets was only a day post-inoculation, and diarrhea lasted for 2-6 days. Piglets' small intestines displayed mild to moderate villous atrophy as well as mild to moderate and multifocal villous fusion (Shen et al. 2012).

Piglets were injected with the human NoV strain GII as part of the experiment. The diarrhea was less severe and self-inductance, lasting for one to three days, and the incubation period ranged from 24 to 48 hours. Additionally, it was found that the virus shed lasted for only 1-4 days. The cytoplasm of the small intestine cells contained the virus antigen. There was multifocal degeneration of the intestinal villi, which affected the morphology of intestinal cells and low-intensity histo-pathological lesions. An additional finding of this research was the rise in enterocytes that had undergone apoptosis (Cheetham et al. 2006).

NoV reduplication might not be limited to intestinal cells. The only norovirus that replicates in vitro among all the latent experimental studies investigated to better understand the mechanism of disease proliferation of noroviruses is the murine NoV. This agent reproduces in bone marrow cell cultures, mouse macrophage cell lines and dendritic cells derived from cultures of macrophages and bone marrow. Recombination-activating gene 2 (RAG2) and signal transducer and activator of transcription 1 (STAT-1) gene knockout mice exhibited hematopoietic cell tropism (macrophages and dendritic cells) and systemic disease development in response to murine NoV-1 infection. Clinical symptoms range from pneumonia and inflamed liver to inflammation in the brain and brain capillaries (Wobus et al. 2004; Scipioni et al. 2008; Karst et al. 2015). Moreover, it is still unknown whether the murine NoVs virus is a potent gut infectious agent of this particular vertebrate (Hsu et al. 2005).

Zoonotic Transmission of Norovirus and One Health Importance

Norovirus is an RNA virus, and many RNA viruses that affect people can also infect other vertebrate hosts in addition to humans because these are zoonotic. Many of those not considered zoonotic is thought to have recently evolved from zoonotic origins in evolutionary terms. Therefore, in the context of one health, norovirus is of particular importance. Man and animal's noroviruses genome has close similarities as well as the advent of recombinant NoV strains in various hosts have been demonstrated by research studies at micro level of environmental and genetic risk factors of noroviruses (Koopmans 2008). Bovine, porcine, canine, and feline genotypes contain the recombinants. It is conceivable that human-animal norovirus recombinants could form, particularly when comparing closely related animal and human genotypes. Multiple genotypes and genogroups of humans and animals can coexist in water, food sources, and filter-feeding shellfish, creating a potential source of co-infection in both species (Villabruna et al. 2019).

Veterinary professionals and the general public have both assessed positive in serological studies for immunoglobins against human NoV (Widdowson et al. 2005; Menon et al. 2013) and immunoglobulins against animal NoV (Farkas et al. 2005). Additionally, molecular research found human Nov. Strains in raw pork meat, cattle, and pig feces, and the

most common strain found recently is more prevalent (GII.4) (Mattison et al. 2007). Furthermore, infection of gnotobiotic calves and piglets with man NoV demonstrated virus duplication and primary-infection (Cheetham et al. 2006; Souza et al. 2008).
This theory has not been proved yet, despite the likelihood that zoonotic transmission exists. More research is required to fully understand the significance of animals serving as reservoirs for human NoV infection because noroviruses are believed to be specifically oriented pathogens to particular vertebrates (Karst et al. 2015).

Diagnosis

Electron microscopy (EM) and real-time polymerase chain reaction (RT-PCR) are two methods used for the sensing of both human and animal NoVs. For the recognition of human(Vinjé 2015), swine (Machnowska et al. 2014) and bovine NoV strains (Jor et al. 2010, Yilmaz et al. 2011) other methods for RT- quantitative (RT-q PCR)-based Nov RNA detection and quantification have been reported. Immunoassays, like the enzyme-linked immunosorbent assay (ELISA), can identify viral foreign bodies or antibodies, both of which are the methods used to create recombinant virus-like particles (Wang et al. 2007; Mauroy et al. 2009.). For the virus diagnosis, other methods can also be used, including immunohistochemistry (Otto et al. 2011) and microarray hybridization (Wang et al. 2007; Scheuer et al. 2013).
The benefits and drawbacks of the methods used for the recognition of NoV infection are shown in the Table 1:

Control Strategies by Considering One Health Approach

The most common symptom of NoV infection in livestock animals is mild to moderate non-hemorrhagic diarrhea. Even when diarrhea has stopped, and animals are exhibiting the signs, the NoV fecal shedding can persist. In this situation, it is important to pay closer attention to the management of the environment and livestock to treat the afflicted animals clinically (O'Brien and Xagoraraki 2019).
Animals in the herd that have a NoV infection and are suspected or proven should be kept apart from the others. The key to managing NoV-induced diarrhea, which is typically a self-recovery infection that clears up within days of exposure, is to replace and maintain adequate levels of fluid and electrolytes. For calves, compared to piglets, fluid therapies are simpler to implement. Piglets may take oral medications designed to restore the hydro electrolytic balance. The use of broad-spectrum antibiotic therapy is advised in cases of severe diarrhea to control secondary infections. Milk after calving that contains maternal antibodies are likely to prevent infection and damage in nursing piglets' guts. Consuming colostrum may have some effect on the bovine NoV infection, even if it does not prevent it, by limiting the spread of infection and lowering the intensity and length of the diarrhea (Otto et al. 2011). To assess the impact of milk after calving on the development of the bovine and swine NoV infections, additional pathogenic studies should be carried out in the field.
Since noroviruses are very enduring in the environment, the development of appropriate science-based risk management policies that adhere to transboundary regulations is thus one of the most crucial factors in the control of norovirus at the interface between humans, animals, and the environment. The FAO, WHO, and OIE have made efforts to incorporate the One Health approach into their tripartite initiative's guiding principles, working closely with academic institutions, intergovernmental institutions, the private sector, nongovernmental organizations, public sectors, and other investors. The effective prevention and control of zoonotic diseases must start with an effective surveillance system, which includes a strong laboratory network. Revaluating the structure, resource allocation, and management of current systems is necessary in order to create a successful One Health implementation plan for boosting capacity at the national, regional, or international levels. Synergies between the human health, animal health, and ecosystem sectors can be developed and sustained with the help of these analyses (Gebreyes et al. 2014).

Prophylactic Measures

Animal infections are not preventable by vaccines. As a result, taking prophylactic measures is essential to prevent the disease. NoV infection and persistence in the environment should be controlled and/or prevented by removing waste, maintaining clean facilities, disinfecting, and taking other sanitary precautions. Since NoV is a waterborne pathogen, appropriate water management procedures should be used. This includes ensuring that the drinking water provided to the animals is of high quality, spotless, and has received an adequate amount of chlorine treatment. Given that NoVs are thought to be potentially zoonotic, public health-oriented management should also be taken into consideration. NoV is enduring in the surroundings and, depending on the circumstances, may not be inactivated by specific drug-oriented substances and heat. The effects of freezing and thawing do not seem to affect NoV (Nims and Plavsic 2013). Heat can reduce the infectivity of NoV by inactivating it, but extensive inactivation requires exposure times of at least 30 minutes and temperatures greater than 56°C (Duizer et al. 2004, Nims and Plavsic 2013). Irrespective of the calicivirus species or strain, higher temperatures (60°C) result in more thorough and consistent inactivation (Nims and Plavsic 2013). Because livestock manure has the potential to be a biofertilizer, it is applied to field land across the world to improve agriculture. Therefore, to lessen the spread of NoV in animal waste and to reduce the spread of manure-borne fecal contamination of the environment; an anaerobic bio-digester system is a tool that can be used to treat livestock

Table 1: Benefits and drawbacks of various diagnostic methods used for detection of NoV infection (Zaczek-Moczydlowska MA et al. 2021)

Diagnostic tests	Benefits	Drawbacks
Electron microscopy	Being able to recognize various virus pathogens	Low-sensitivity (limit of detection: 106 enteric virus particles per milliliter of fecal sample), lacking the ability to distinguish NoV from other small round enteric viruses, need qualified experts, costly equipment that is not frequently found in microbiological labs, time-consuming.
NGS	Extremely sensitive. Specificity is remarkably high. Virus detection and description in a single assay. Detection of microbial content in a single test. It may help to identify the infectious agent causing unexplained cases of suspected viral gut ailments.	Veterinary diagnostic labs lack access to costly equipment. Needs competent and skilled personnel.
Enzyme immunoassays	Ability to recognize soluble antigens as well as viral particles. A direct ELISA was demonstrated to be a pinpoint appropriate method (limit of sensing and 0.025ng of capsid protein viral antigen diluted 1:10,000 times within the fecal samples). Valuable for quickly screening more than one sample.	High specificity in VLP-based EIAs (underestimation of results may result from antigenically distinct NoV strains in circulation). Pig NoV VLP-based antibody ELISA shows a reaction with human NoV antibodies.
RT-q PCR	An improvement in sensitivity and specificity, even when compared to traditional RT-PCR assays. Eliminate the need for agar rose gel or hybridization analyses. Reduced sample carrying (lower risk of cross-contamination). Permit the measurement of the quantity of virus nucleic acid on a sample. Swift test.	There is a need for RT-q PCR equipment. The materials are costly. Virus genotyping is not possible with this method.

manure in order to provide safe bio-fertilizers, even though it is unclear whether gut viruses are effectively inactivated by anaerobic bio-digestion (Otto et al. 2011).

Conclusion

Bovine noroviruses are frequently found in cattle and occasionally at high frequency in cases of diarrhea in various countries, despite the fact that they have been studied much less than other viruses that are known to be the cause of NCD (neonatal calf diarrhea), such as rotavirus and coronavirus. The development of appropriate science-based risk management policies that adhere to transboundary regulations is thus one of the most crucial factors in the control of norovirus at the interface between humans, animals, and the environment. Animals in the herd that have a NoV infection and are suspected or proven should be kept apart from the others. The key to manage NoV-induced diarrhea, which is typically a self-recovery infection that clears up within days of exposure, is to replace and maintain adequate levels of fluid and electrolytes. The effective prevention and control of zoonotic diseases must start with an effective surveillance system, which includes a strong laboratory network. Revaluating the structure, resource allocation, and management of current systems is necessary in order to create a successful One Health implementation plan for boosting capacity at the national, regional, or international levels.

REFERENCES

Castells M et al., 2020. Detection, risk factors and molecular diversity of norovirus GIII in cattle in Uruguay. Infection, Genetics and Evolution 86: 104613. doi:https://doi.org/10.1016/j.meegid.2020.104613

Caul EOJJOCP, 1996. Viral gastroenteritis: small round structured viruses, caliciviruses and astroviruses. Part I. The Clinical and Diagnostic Perspective 49(11): 874.

Cheetham S et al., 2006. Pathogenesis of a genogroup II human norovirus in gnotobiotic pigs. Journal of virology 80: 10372-10381.

Duizer E et al., 2004. Inactivation of caliciviruses. Applied and Environmental Microbiology 70: 4538-4543.

Farkas T et al., 2005. Seroprevalence of noroviruses in swine. Journal of Clinical Microbiology 43: 657-661.

Frange P et al., 2012. Prevalence and Clinical Impact of Norovirus Fecal Shedding in Children with Inherited Immune Deficiencies. The Journal of Infectious Diseases 206(8): 1269-1274.

Gebreyes WA et al., 2014. The global one health paradigm: challenges and opportunities for tackling infectious diseases at the human, animal, and environment interface in low-resource settings. PLoS Neglected Tropical Diseases 8(11): e3257.

Hall G et al., 1984. Lesions of gnotobiotic calves experimentally infected with a calicivirus-like (Newbury) agent. Veterinary Pathology 21: 208-215.

Hsu CC et al., 2005. Development of a microsphere-based serologic multiplexed fluorescent immunoassay and a reverse transcriptase PCR assay to detect murine norovirus 1 infection in mice. Clinical and Vaccine Immunology 12: 1145-1151.

Jor E et al., 2010. SYBR Green based real-time RT-PCR assay for detection and genotype prediction of bovine noroviruses and assessment of clinical significance in Norway. Journal of Virological Methods 169: 1-7.

Jung K et al., 2014. Pathogenesis of GIII. 2 bovine norovirus, CV186-OH/00/US strain in gnotobiotic calves. Veterinary Microbiology 168: 202-207.

Karst SM et al., 2015. The molecular pathology of noroviruses. The Journal of Pathology 235: 206-216.

Machnowska P et al., 2014. Detection and characterization of potentially zoonotic viruses in faeces of pigs at slaughter in Germany. Veterinary Microbiology 168: 60-68.

Matthews JE et al., 2012. The epidemiology of published norovirus outbreaks: a review of risk factors associated with attack rate and genogroup. Epidemiology and Infection 140): 1161-1172.

Mattison K et al., 2007. Human noroviruses in swine and cattle. Emerging Infectious Diseases: 13: 1184.

Mauroy A et al., 2009. Epidemiological study of bovine norovirus infection by RT-PCR and a VLP-based antibody ELISA. Veterinary Microbiology 137: 243-251.

Menon VK et al., 2013. Exposure to human and bovine noroviruses in a birth cohort in southern India from 2002 to 2006. Journal of Clinical Microbiology 51: 2391-2395.

Nims R and Plavsic M, 2013. Inactivation of caliciviruses. Pharmaceuticals 6: 358-392.

Otto PH et al., 2011. Infection of calves with bovine norovirus GIII. 1 strain Jena virus: an experimental model to study the pathogenesis of norovirus infection. Journal of Virology 85: 12013-12021.

O'Brien E and Xagoraraki I, 2019. A water-focused one-health approach for early detection and prevention of viral outbreaks. One Health 7: 100094.

Patel MM et al., 2008. Systematic literature review of role of noroviruses in sporadic gastroenteritis. Emerging Infectious Diseases 14(8): 1224-1231.

Scheuer KA et al., 2013. Prevalence of porcine noroviruses, molecular characterization of emerging porcine sapoviruses from finisher swine in the United States, and unified classification scheme for sapoviruses. Journal of Clinical Microbiology 51: 2344-2353.

Scipioni A et al., 2008. Animal noroviruses. The Veterinary Journal 178: 32-45.

Shen Q et al., 2012. Recombinant porcine norovirus identified from piglet with diarrhea. BMC Veterinary Research 8: 1-6.

Siebenga JJ et al., 2009. Norovirus illness is a global problem: emergence and spread of norovirus GII. 4 variants, 2001–2007. The Journal of Infectious Diseases 200(5): 802-812.

Souza M et al., 2008. Pathogenesis and immune responses in gnotobiotic calves after infection with the genogroup II. 4-HS66 strain of human norovirus. Journal of Virology 82: 1777-1786.

Villabruna N et al., 2019. Animals as reservoir for human norovirus. Viruses 11: 478.

Vinjé J, 2015. Advances in laboratory methods for detection and typing of norovirus. Journal of Clinical Microbiology 53: 373-381.

Wang QH et al., 2007. Porcine enteric caliciviruses: genetic and antigenic relatedness to human caliciviruses, diagnosis and epidemiology. Vaccine 25: 5453-5466.

Widdowson MA et al., 2005. Detection of serum antibodies to bovine norovirus in veterinarians and the general population in the Netherlands. Journal of Medical Virology 76: 119-128.

Wobus CE et al., 2004. Replication of Norovirus in cell culture reveals a tropism for dendritic cells and macrophages. PLoS Biology 2: e432.

Yilmaz H et al., 2011. First report on the phylogeny of bovine norovirus in Turkey. Archives of Virology 156: 143-147.