UNIVERSITI PUTRA MALAYSIA

REVIEW ON DESCRIPTIVE ANALYSIS OF NOROVIRUS INFECTION IN PIGS, DOGS AND CATS

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FPV 2021 7

REVIEW ON DESCRIPTIVE ANALYSIS OF NOROVIRUS INFECTION IN PIGS, DOGS AND CATS

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A project paper submitted to the

Faculty of Veterinary Medicine, Universiti Putra Malaysia

In partial fulfilment of the requirement for the

DEGREE OF DOCTOR OF VETERINARY MEDICINE

Universiti Putra Malaysia

Serdang, Selangor Darul Ehsan.

DECEMBER 2021

DEDICATION

This thesis is especially dedicated to:

My supportive supervisors

Prof. Dr Siti Suri Binti Arshad

Assoc. Prof. Dr Ooi Peck Toung

Dr. Nor Yasmin Abd Rahaman

Dr. Norfitriah Mohamed Sohaimi

Dr. Nurfazila Saulol Hamid

Assoc. Prof. Dr Gayathri Thevi Selvarajah

Dr. Michelle Fong Wai Cheng

My loving parents

Yii Ing Ho and Tang Geong Lung

And

DVM2022 Batchmates

ACKNOWLEDGEMENT

I would want to offer my genuine and heartfelt gratitude to everyone who helped me complete my final year project successfully.

First and foremost, I owe a debt of gratitude to my supervisor, Professor Dr Siti Suri binti Arshad, for providing me with vital guidance and constructive ideas that guided me in the right way in the completion of my research. I would also like to express my gratitude to Assoc. Prof. Dr. Ooi Peck Toung, my co-supervisor, for his constant support and valuable life lessons throughout my final year project trip. I would like to acknowledge Dr. Nor Yasmin Abd Rahaman for her time and knowledge in helping me to provide advice to my project. I would want to use this time to express my gratitude to Dr. Norfitriah Mohamed Sohaimi and Dr. Nurfazila Saulol Hamid, who guided me through my review. I would like to extend my gratitude to A.P. Dr. Gayathri Thevi Selvarajah who is willing to spend her precious time to provide me extensive personal and professional guidance in this review.

Next, I would like to take this opportunity to thank Dr Michelle Fong Wai Cheng who helped and gave me personal support during my review. My sincere thanks also go to my DVM 22 coursemates who have been working together with me throughout this project and assisted me in various aspects.

Last but not least, I sincerely thank everyone who directly or indirectly assisted me in this project. This project would not be a success without each and every one of them.

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ABBREVIATIONS

bp	base pairs
CNV/ CaNoV	canine norovirus
CDC	centers for disease control and prevention
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assays
FCV	feline coronaviruses
G	genogroup
Gn	gnotobiotic
HBGA	histo-blood group antigens
HGMT	human gut microbiota-transplanted
HuNoV	human norovirus
Ig	immunoglobulin
kb	kilobase
NoV	norovirus
NS	non-structural
nt	nucleotide
ORF	open reading frame
P	protrusion
PCR	polymerase chain reaction
PID	post inoculation day

PoNoV	porcine norovirus
RdRp	RNA-dependent RNA polymerase
RNA	ribonucleic acid
rpm	revolutions per minute
RT-PCR	reverse transcriptase polymerase chain reaction
SRSV	small round structured virus
USA	United States of America
VLP	virus like particles
VP	viral protein

ABSTRAK

ULASAN MENGENAI ANALISIS DISKRIPTIF JANGKITAN NOROVIRUS PADA BABI, ANJING DAN KUCING

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Norovirus tergolong dalam keluarga Caliciviridae dan telah dikenal pasti sebagai penyebab utama wabak gastroenteritis akut pada manusia dari semua peringkat umur di seluruh dunia. Kedua-dua haiwan yang tidak sihat secara klinikal dan tanpa gejala berkemungkinan diuji positif untuk norovirus. Walau bagaimanapun, tiada laporan yang jelas dan komprehensif

mengenai norovirus haiwan yang telah dijalankan sehingga kini. Tambahan pula, terdapat maklumat terhad tentang kelaziman norovirus dalam perumah haiwan tempatan. Objektif kertas ini adalah untuk mengkaji dan menganalisis insiden, pengedaran dan status norovirus yang didokumenkan dalam babi, anjing dan kucing yang sihat dan sakit klinikal. Penemuan kajian ini akan berguna dalam hala tuju penyelidikan norovirus pada masa hadapan. Kertas kerja ini mengkaji literatur dari 1998 hingga 2021 terdiri daripada takungan haiwan, situasi norovirus global, prosedur diagnostik, dan kemungkinan laluan penghantaran norovirus di kalangan manusia dan haiwan. Norovirus haiwan babi, anjing dan kucing dikesan di seluruh dunia termasuk Asia, Eropah, Amerika serta New Zealand. Reverse transcriptase polymerase chain reaction (RT-PCR) ialah kaedah pengesanan yang paling biasa untuk norovirus pada haiwan. Makalah ini juga membincangkan bukti antibodi/antigen norovirus manusia dalam populasi haiwan. Walau bagaimanapun, berdasarkan kajian semasa, mungkin masih terdapat bukti yang tidak mencukupi untuk mengesahkan potensi penghantaran norovirus daripada haiwan kepada manusia dan sebaliknya.

Kata kunci: Norovirus, babi, anjing, kucing, pengesanan antigen dan antibodi.

ABSTRACT

REVIEW ON DESCRIPTIVE ANALYSIS OF NOROVIRUS INFECTION IN PIGS, DOGS AND CATS

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Noroviruses belong to the Caliciviridae family and have been identified as a leading cause of acute gastroenteritis outbreaks in humans of all ages all over the world. Both clinically unwell and asymptomatic animals are likely to test positive for norovirus. However, there is no clear and comprehensive report on animal noroviruses that has been conducted to date.

Furthermore, there is limited information on norovirus prevalence in local animal hosts. The objective of this paper is to review and analyse the documented incidence, distribution and status of norovirus status in healthy and clinically ill pigs, dogs and cats. The findings of this study will be useful in future direction of norovirus research. This paper reviewed literature from 1998 to 2021 comprises animal reservoirs, global norovirus situation, diagnostic procedures, and likely norovirus transmission routes among people and animals. Animal norovirus of pigs, dogs and cats are detected worldwide which include Asia, Europe, America and in New Zealand. Reverse transcriptase polymerase chain reaction (RT-PCR) is the most common method of detection for norovirus in animals. The paper also discusses the evidence of human norovirus antibodies/antigens in animal populations. However, based on current studies, there may still be insufficient evidence to validate the potential transmission of norovirus from animal to human and vice versa.

Keywords: Norovirus, pigs, dogs, cats, antigens and antibodies detection.

INTRODUCTION

1.1 Norovirus

Norovirus infections are usually severe and short-lived. Noroviruses are categorised as Category B biodefense agents because they are highly gastroenteritis, can cause severe sickness, are exceedingly stable in the environment and can withstand standard disinfectants (Karst, 2010). In the United States, the sickness is most commonly diagnosed from November until the end of May which is during the winter season. As a result, the sickness is also known as "winter vomiting disease." Noroviruses infect a wide range of hosts, causing diseases such as digestive tract infections, systemic diseases, and haemorrhagic disease (Peñaflor-Téllez *et al.*, 2019). G (Genogroup) II (pigs), GIII (small and large domestic ruminants), GIV (lion, dog, cat), GV (mice), GVI (dog, cat), and GVII (dog, cat) are the different types of NoVs found in animals (Di Martino *et al.,* 2019).

For porcine norovirus, the sequences were found in genogroup II of human small round structured viruses (SRSVs), but in the evolutionary tree of caliciviruses, they formed a subgroup (Sugieda *et al.*, 1998). Moreover, caliciviruses were discovered in the stool samples of pigs and calves using electron microscopy shortly after the Norwalk virus was identified (Bridger, 1980). Finisher pigs are the most commonly infected with norovirus. Pigs from high-income countries have been shown to be infected with norovirus (Scheuer *et al.*, 2013). For example in the United Kingdom, Germany, Japan, and the Netherlands, NoV ribonucleic acid (RNA) was found in the faeces of pigs. Furthermore, a porcine norovirus detected on pig farms in Korea is similar to NoV genotypes GII-11, GII-18, and GII-21

(Keum *et al.*, 2009). 58 percent of faecal samples taken from asymptomatic adult pigs in Brazil also proved positive for norovirus (Silva *et al.*, 2015).

Canine norovirus (CNV) has previously been found as having four genotypes (GIV.2, GVI.1, GVI.2, and GVII) (Villabruna *et al.*, 2019). GIV and GVI animal noroviruses appear to have influence on disease in felines also (Ford-Siltz *et al.*, 2019). As for human norovirus, regarding an epidemic of norovirus gastroenteritis in an older adults home in 1983, dogs were first mentioned as probable zoonotic vectors of human norovirus (HuNoV). Dogs may be responsible for transmitting human noroviruses according to several studies (Caddy *et al.*, 2015). In 2012, three dogs' faeces were found to contain the main HuNoV genogroup GII (Summa *et al.*, 2012).

One of the most frequent viral infections in cats is feline calicivirus that can cause a respiratory infection in cats, which is frequently accompanied by ocular discharge and ulcerative stomatitis. The emerging circulation of noroviruses among cats was when NoVs RNA was identified in the faeces of cats with enteritis from a feline shelter in New York State (Pinto *et al.*, 2012). GIV.2 NoVs detection rates were reported in subsequent molecular analyses in cats with 1.2% in Japan (Soma *et al.,* 2015), 2.8% in Brazil (Castro *et al.,* 2015), and 6.2% in Italy (Di Martino *et al.*, 2016). NoVs are also found in carnivores, according to several research (Pinto *et al.*, 2012). NoVs GIV.2 and GVI.2, can be found in both cats and dogs as well (Di Martino *et al.*, 2016).

1.2 Objective and Justification

Noroviruses are to account for at least 95% of viral outbreaks and more than half of all outbreaks worldwide (Karst, 2010). HuNoV produces acute diarrhoea, vomiting, and stomach cramps in people, and the sickness lasts for about 28 to 60 hour (Glass *et al.*, 2009). In 1968, the first outbreak occurred at a school in Norwalk, Ohio, United States (Communicable Diseases Network Australia, 2010). According to a recent analysis of diagnostic trials testing for norovirus outbreaks in clinical situations, norovirus diseases are common for about one million hospitalizations and 200,000 fatalities in young children in developing nations each year (Patel *et al.*, 2008).

The raised focus on possible reservoirs of norovirus as zoonotic transmission between humans and animals is due to the close relation of human and animal norovirus (Wolf *et al.*, 2009). For instance, human and swine NoVs have tight genetic and antigenic links, showing their potential for zoonotic transmission and as reservoirs for the establishment of novel pandemic human strains (Wang *et al.*, 2005). Various genotypes of norovirus have been found in different species of animals like pigs, cattle, and dogs (Charoenkul *et al.*, 2020). Noroviruses widely distributed in nature, such as pigs, dogs, and cats, are concerned with human viruses. They are divided into two groups which consist of GII and GIV, genogroup for porcine norovirus and feline and canine norovirus respectively (Vinjé, 2015). The frequent discovery of new norovirus genotypes as well as norovirus strains that are the same like humans in faecal specimens from sick and healthy livestocks has sparked concern regarding animals' potential role as zoonotic reservoirs for these strains (Sugieda *et al.*, 1998).

Norovirus can be exclusively found in a faecal material sample of asymptomatic pigs (Wang *et al.*, 2005; 2006) or pigs with a history of diarrhoea (Reuter *et al.*, 2007) and gastroenteritis. Recent preliminary studies on detection of norovirus in healthy animals show no antigen amplification (Tan *et al.*, 2020) suggesting until now, there is no proof of norovirus infection in healthy animals in Malaysia. Norovirus status in animals remains ambiguous. The main objective of this study is to review the distribution and status of norovirus in animal hosts worldwide. To date, the role of animal NoVs in human infections is unknown and yet to be clarified. Therefore, animals including cats, dogs, and pigs that are healthy and asymptomatic, clinically ill and show symptoms especially diarrhoea are included for this review.

Norovirus can be transmitted through faecal and oral routes consequently causing acute gastroenteritis. The norovirus detection rates in stools of animals with diarrhoea were positively higher compared to samples of stools from non-diarrhoea animals (Sokel *et al.*, 2019). However, there are some studies showing that asymptomatic and healthy animals also have the potential of having norovirus infection. For instance, the majority of asymptomatic finishing pigs tested positive for norovirus (Shen *et al.*, 2012) and NoV has been found in healthy dogs as well (Mesquita *et al.*, 2010). Therefore, clinically ill and asymptomatic animals are both likely to show a positive norovirus detection rate. However, until now there is no clear and confirmatory report has been performed on animals. Moreover, there are few reports on prevalence of norovirus in local animal hosts. The results of this study will further assist in future research of norovirus. This study reviewed norovirus

literature from 1998 to 2021, known animal reservoirs for norovirus, focusing on the norovirus scenario worldwide, diagnostic methods used and possible route of transmission of norovirus among humans and animals worldwide.

The study was conducted with the following objectives:

1. To discuss the virology, transmission, classification, clinical signs and diagnosis of norovirus in pigs, dogs and cats.
2. To review and analyse the detection rate, distribution and status of norovirus infection in pigs, dogs and cats worldwide.

METHODOLOGY

This is a narrative review on descriptive analyses of norovirus infection in pigs, dogs and cats. The search engines used in the review include the Scopes, Pubmed and Google scholar where related full papers, abstracts, reports, proceedings and thesis were extracted. Topics were focused on sources that related to norovirus infection in pigs, dogs and cats. Total of 144 papers from 1991 to 2001 had been reviewed in this study. Only English language papers were chosen and there is no territory limitation. Keywords that used in search engines were as follows (pig OR pigs OR swine OR porcine OR cat OR cats OR feline OR dog OR dogs OR canine) AND (norovirus* OR norwalk) AND (molecular OR diagnosis OR test OR detection OR identification OR PCR OR isolation OR immunoassay OR hybridization OR hybridisation OR ELISA OR genomics).

LITERATURE REVIEW

3.1 Overview of Norovirus

Noroviruses (NoVs) are previously known as Norwalk-like viruses and they were first identified in 1972 (Doblin *et al.*, 1972). Norovirus is a member of the caliciviridae family that consist of 5 genus which are vesivirus, lagovirus, nebovirus, norovirus and sapovirus (Soma *et al.*, 2015). Noroviruses are commonly causing acute gastroenteritis in humans (Glass *et al.*, 2009). Noroviruses (NoVs) are small, circular, non-enveloped and positive-strand RNA viruses with dimensions of 27-38 nm that contain a single viral capsid protein (Kobayashi *et al.*, 2016).

Noroviruses exist in many different genotypes and polymerase groups due to the rapid evolution of its genome (Kobayashi *et al.*, 2016). NoV is divided into five genotypes depending on the composition of the primary structural capsid protein (VP1) (genotype I [GI] to genotype V [GV]) (Mei *et al.*, 2011). NoV has been further split into 8 GI genotypes and 21 GII genotypes based on the entire VP1 sequence, and 14 GI genotypes and 31 GII genotypes based on the partial sequence of RNA-dependent RNA polymerase (RdRp), by typing-tools (Kroneman *et al.,* 2011). Some new noroviruses have just been discovered in the past few years, the number of genogroups has been increased to ten (GI-GX) (Chhabra *et al.,* 2019). The GII strains are the most common in individuals around the world (Green, 2013).

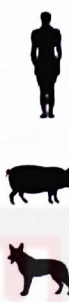
Genogroups	I	II	III	IV	V	VI	VII	VIII	IX	X
Hosts										

Table 1: Classification of 10 genogroups (Genogroup I to X) of noroviruses based on their sequence diversity of capsid protein VP1

More than 90% of nonbacterial outbreak gastroenteritis is triggered by Norwalk-like caliciviruses (Noroviruses) around the world (Karst *et al.*, 2003). Norovirus has appeared as a major causal agent, and it is now recognized as the leading issue of non-acute gastroenteritis in people of all ages. NoV-related outbreaks are common in places like hospitals, cruise ships, military and vacation camps, nursing homes, childcare, hotels, and catered events (Zainazor *et al.*, 2010). Norovirus is thought to be the cause of more than 23 million gastroenteritis infections in the United States annually, accounting for over 60% among all acute gastroenteritis episodes (Mead *et al.*, 1999). Norovirus is extremely contagious in both human and animal and spread via person to person, animal to animal, fomites exposure or contaminated food and water (Wolf *et al.*, 2009). Several characteristics that enhance effective norovirus spread through with a range of modalities include a high titre of shedding

by affected individuals, a low infectious dosage, and environmental stability (Barclay *et al.*, 2014).

Other than pigs, dogs and cats, noroviruses from various genogroups affect a large number of species, including livestock such as cows and sheep, as well as sea mammals and rodents (Villabruna *et al.*, 2019). Noroviruses GIII have also been found in cows and sheep. Besides, noroviruses GV have been identified in mice and rats. In cats, feline noroviruses GIV and GVI are detected (Ford-Siltz *et al.*, 2019). Particularly the GI, GII, and GIV have been shown to infect people, with GII seems to be the most common, accounting for more than 95% of all infections in humans (White, 2014).

3.1.1 Porcine Norovirus

Pigs are infected with NoV GII, which is the most common cause of acute viral gastroenteritis in people. Human noroviruses (HuNoVs) were genetically and antigenically related to specific porcine norovirus (PoNoV) strains (Wang *et al.*, 2007), raising threats to public health about their possibility for zoonotic transmission and as reservoirs for the introduction of emerging outbreak human strains (Wang *et al.*, 2005). PoNoVs were initially discovered in 1997 in Shizuoka Prefecture, Japan, when the GII.11 genotype was found in asymptomatic pigs (Sugieda *et al.* 1998). Pigs of various ages can be infected with porcine noroviruses. Noroviruses were found in sucklings, weanlings, and fattening pigs (Chao *et al.,* 2012). HuNoV inoculated in human gut microbiota-transplanted (HGMT) gnotobiotic (Gn) pigs led to a greater HuNoV shedding on post inoculation day (PID) comparing to germ-

free Gn pigs, as evidenced by a considerably longer average length of viral shedding (Lei *et al.*, 2019), potentially for zoonotic transmission of noroviruses (NoVs). GII consists of three genotypes (GII.11, GII.18, and GII.19) which can be found in pigs faeces (Ford-Siltz *et al.*, 2019). Furthermore, porcine NoV was discovered in a number of additional countries, including South Korea (Park *et al.*, 2021), Italy (Cavicchio *et al.*, 2020), United States (Craig *et al.*, 2019) and Japan (Okada *et al.*, 2019).

11 out of 18 countries detect porcine norovirus in pigs by RT-PCR as indicated by the blue colour bar (Figure 1). Canada has the highest percentage of detection rate of porcine norovirus (L'Homme *et al.*, 2009). Amongst diagnostic assays used, 3 out of 16 countries had detected porcine norovirus in pigs through ELISA as indicated by the blue colour bar (Figure 2). Among all countries, the USA has the highest detection rate (Farkas *et al.*, 2005).

PoNoVs VP1 genotypes GII.11, GII.18, and/or GII.19 have been found in both seemingly asymptomatic and diarrhoeic pigs in Japan (Nakamura *et al.*, 2010). Porcine norovirus can cause diarrhoea in piglets, according to an experiment with miniature pigs infected with this porcine NoV positive faecal sample (Shen *et al.*, 2012). In the ORF 1, a probable recombination activity was discovered after a whole genome analysis of first porcine NoV in Europe (Laconi *et al.*, 2020). Even though recombination episodes in other genomic locations have been documented (Motomura *et al.*, 2010), this event usually happens in the ORF1/ORF2 overlap region (Bull *et al.*, 2007). Recombination occurrences between NoV genotypes have been identified, and they pose a significant hazard to human and veterinary health because emerging recombinants may have antigenic characteristics that

differ from their parental strains (Eden *et al.*, 2013). Swine were also found to have human noroviruses (HuNoVs) (Nakamura *et al.,* 2010), suggesting that they are susceptible to HuNoVs.

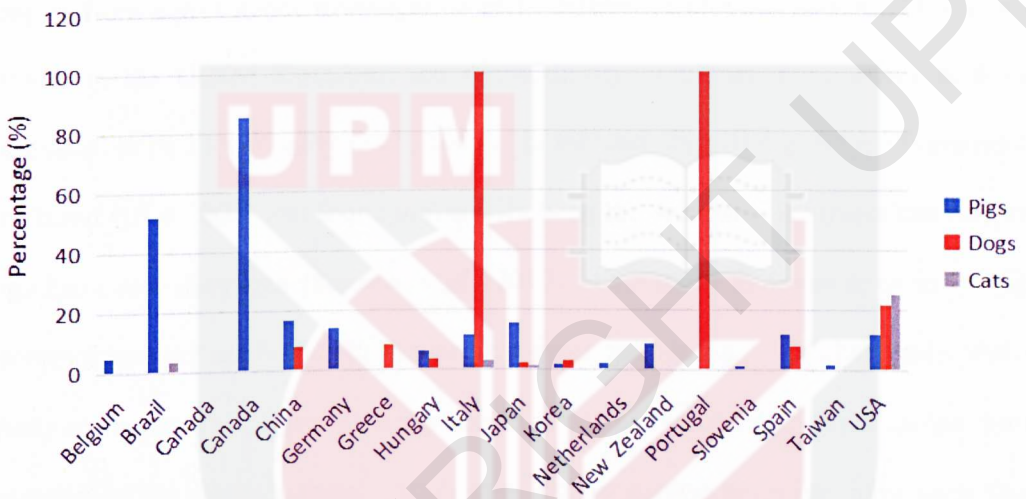


Figure 1: Animal norovirus antigen detection in animal hosts based on report from 18 countries (Data is obtained based on the summary of Appendix 1)

3.1.2 Canine Norovirus

In 2007, canine norovirus (CaNoV) was first discovered in a dog with enteritis in Italy and the strain was labelled GIV. 2 genotype (Martella *et al.*, 2008). CaNoVs were first discovered in faeces specimens from dogs in Portugal in 2007, and since then, these viruses have been found in dogs from all around Europe and Asia (Mesquita *et al.*, 2010). About 50% (9/18) countries in this review detect canine norovirus in dogs that are demonstrated by

orange colour bars (Figure 1). Italy (Martella *et al.*, 2008) and Portugal (Mesquita *et al.*, 2012) show the highest cases of norovirus dogs (Figure 1).

Seroprevalence for CaNoV in 2014 was predicted to be 39 percent in dog serum samples from a prevalence investigation of 14 different European nations (Mesquita *et al.*, 2014). In the United Kingdom, the seropositivity of human noroviruses in dogs was discovered to be 13% (Caddy *et al.*, 2013). In Finland, the GII.4 genotype (variants GII.4-2006b and GII.4-2008) was found in dogs, showing that human noroviruses can be spread to dogs and cause diarrhoea (Summa *et al.*, 2012). One study that was done in Portugal on seroprevalence of antibodies to canine norovirus genogroup VI. The results show that veterinarians have a 4 times higher percentage of seropositivity towards canine norovirus compared to the control group. Antibodies against canine norovirus have been found in humans, including veterinarians who have been exposed to the virus on a regular basis (Mesquita *et al.*, 2013). The presence of a NoV-positive dog in the same household has been linked to an increased risk of NoV seropositivity in humans (Peasey *et al.*, 2004). CaNoVs' introduction could be a public health problem since pets are an important part of family life in most industrialized nations, and their intimate interaction with people necessitates extra caution when it comes to a possible zoonotic pathogen reservoir (Summa *et al.*, 2012). In accordance with Figure 2, canine norovirus in dogs has been reported in 81% of the total countries in this review that are represented by orange color bars and cases are highest in Finland (Mesquita *et al.*, 2014).

Dogs that have potential to HuNoV infection must exhibit histo-blood group antigens (HBGAs) in their gastrointestinal tracts. HBGAs are important for attachment factors of the first stage of HuNoV infestation. In fact canine blood types are unrelated to human blood types, and canine red blood cells are not agglutinated by HuNoV (Estes *et al.*, 2003). However, some research discovered that dogs do express HBGAs in their saliva and on the surface of intestinal epithelial cells (Caddy *et al.*, 2014).

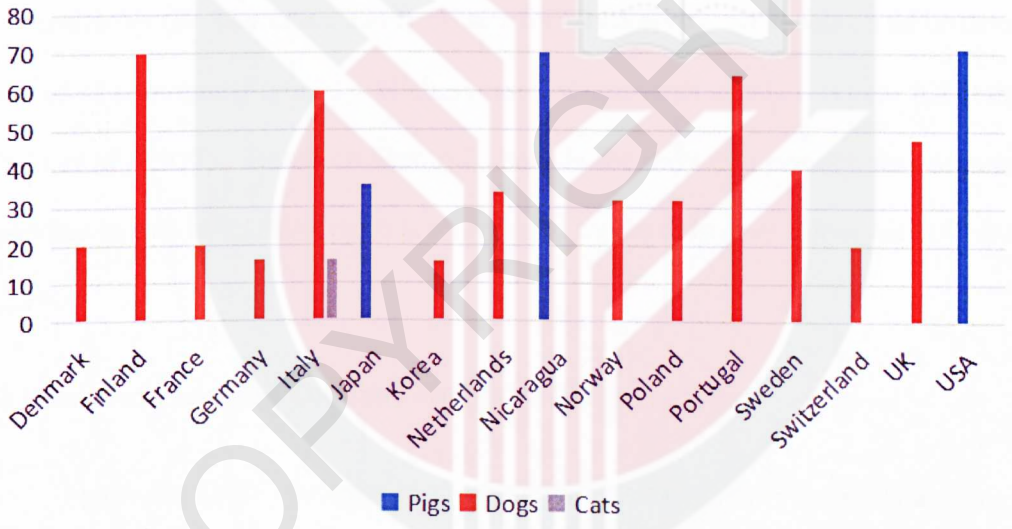


Figure 2: Animal norovirus antibody detection in animal hosts as reported in 16 countries (Data is obtained by summarising information in Appendix 1)

3.1.3 Feline Norovirus

An epidemic of diarrhoea and vomiting in adult cats in Germany in 1987 yielded Norwalk-like 27-nm virus particles that were clearly differentiated from feline coronaviruses

(FCVs) (Humphrey *et al.*, 1984). Feline Norovirus (NoV) strains were very identical to the first found GIV NoV strains of captive lion cubs with severe haemorrhagic enteritis sequencing analysis in Italy (Pinto *et al.*, 2012). NoVs genetically similar to the lion NoV were later discovered in the faeces of dogs suffering from diarrhoea in Italy and Greece (Martella *et al.,* 2008). The lion and human Alphatron- like NoVs, were identified as a separate genotype (GIV.2) within GIV based on the full-length VP1 (GIV.1) (Zheng *et al.*, 2006). Cluster (pol C) strains in canine NoVs have shown recombination similar to that seen in feline NoVs (Bodnar *et al.*, 2017). While for feline norovirus in cats could be detected in 4 out of 18 countries (Figure 1). Highest cases of norovirus in cats was detected in the USA (Pinto *et al.*, 2012). Based on Figure 2, Italy is the only one country that detects feline norovirus in cats by ELISA which is represented by the only grey colour bar (Di Martino *et al.*, 2010).

3.2 Virus Structure and Genome, Molecular Characteristics

Norovirus (NoV) belongs to the Caliciviridae family of viruses (Nakamura *et al.,* 2010). Distinctive cup-like surface is apparent on the surface of norovirus which gave rise to the term "calicivirus". The capsid protein is found on the virions' cup-like surface., which is made up of 180 monomers and is termed as virion protein 1 (VP1), has two domains: the shell (S) and the protrusion (P) domain, which is further broken into P1 and P2 subdomains (Rohayem *et al.*, 2010). 180 capsid molecules are grouped into 90 dimers with a triangulation number (T) = 3 icosahedral symmetry (Prasad *et al.*, 1994), with two unique dimer types forming the higher-order structure (Prasad *et al.*, 1999). NoV is genetically heterogeneous,

with molecular characterisation based on incomplete or complete capsid or RNA-dependent RNA polymerase (RdRp) sequences now classifying it into genogroups I (GI) to GV (Vinjé *et al.*, 2003). The capsid of the virus causes disease and protects viral RNA and deoxyribonucleic acid (DNA) genome (Martella *et al.*, 2007).

Human noroviruses are RNA viruses that are highly infectious and genetically varied (Nelson *et al.*, 2018). After evaluating the amino acid sequences for the main capsid protein of 164 NoV strains, there are 29 genetic clusters (genotypes) in 5 genogroups (Zheng *et al.*, 2006). After whole capsid sequence analysis of 31 genotypes in GI and GII, 23 genotypes were found belonging to 25 clusters. G1 contains from 1- 12 while G2 involves 1-17 (Karst *et al.*, 2003). According to partial capsid sequences of region C, both GIII and GIV have 1 cluster (Fankhauser *et al.*, 2002). Humans can be infected with norovirus GI, GII, and GIV to cause acute gastroenteritis (Vinjé *et al.*, 2004). Norovirus GV can also be identified in humans and the most common cause of recent acute gastroenteritis in humans is NoV GII (Nakamura *et al.,* 2010).

NoV virions have a single-stranded, positive-sense RNA genome of 7.5 to 7.7 kb and are tiny circular virions with a diameter of 27–35 nm. Genome of norovirus consists of 3 overlapping open reading frames (ORFs) (Bull *et al.*, 2005). ORF1 encodes a single polyprotein that is divided into six viral non-structural (NS) proteins (NS1/2, NS3, NS4, NS5, NS6, and NS7) including partial RNA-dependent RNA polymerase (RdRp) via proteolytic cleavage (Sosnovtsev *et al.*, 2006). ORF2 encodes the only significant structural protein in NoVs (Karst *et al.*, 2004). The VP1 capsid protein is structured into a well-conserved interior

shell (S) domain and a protruding (P) domain, resulting in dimeric VP1 arches. The P domain is even further segmented into a P1 stalk subdomain and a hyper variable surface-exposed P2 subdomain that is found near the arches' tips (Prasad *et al.,* 1994). VP2 is a small structural protein encoded by ORF3 (Karst *et al.*, 2004). Translation of ORF4 in murine norovirus is responsible for the production of virulence factor 1 (VF1) protein (McFadden *et al.*, 2011). There is no difference of ORF in nororvirus amongst pigs, dogs and cats in terms of function.

3.3.1 Clinical Manifestations and Pathology in Human

Norovirus illnesses produce diarrhoea in some people and vomiting in others, while around a third of the respondents remain normal. The sickness usually starts with vomiting, followed by stomach pains, fever (in 37 to 45 percent of patients), watery diarrhoea, and other related symptoms like headache, shivering, and muscle aches after a 10- to 51-hour incubation period (Glass *et al.*, 2009). In nosocomial outbreaks and among children less than 11 years of age, the sickness typically takes 2 to 3 days, but it can remain prolonged (4 to 6 days) in nosocomial outbreaks and among kids younger than 11 years of age (Lopman *et al.*, 2004). Virus can be excreted in low titers for up to 8 weeks in formerly healthy individuals, including more than a year in immunocompromised patients and those who have had transplantation (Atmar *et al.*, 2008). There have been reports of deaths linked to epidemics of gastroenteritis among the elderly in nursing homes (CDC, 2007). In the United Kingdom, an estimated 80 people over the age of 64 die each year because of norovirus infestations (Harris *et al.,* 2008). Norovirus infection has been linked to necrotizing enterocolitis in

infants, benign seizures in newborns, and inflammatory bowel disease exacerbations in paediatric patients, according to latest findings (Chen *et al.*, 2009).

3.3.2 Clinical Manifestations and Pathology in Animal

Noroviruses have been found in non-human animals such as pigs, cows, lambs, cats, dogs, rats, and mice (Pinto *et al.*, 2012). In almost every case where a clinical link can be found, infection causes acute gastroenteritis with diarrhoea (Karst *et al.*, 2015). Clinical signs usually appear 19–24 hours after infection (hpi) and include anorexia, vomiting, lethargy, and copious diarrhoea that can last up to 10 days and cause up to 15% loss of weight (Almeida *et al.*, 2018). Animal noroviruses have been useful models for studying the biology of human noroviruses (Vashist *et al.*, 2009). Norovirus antibodies have also been discovered in captive young macaques, though it is unknown if infection causes illness (Farkas *et al.*, 2010). In 1984, the prototype bovine norovirus was reported as the cause of diarrhoea in calves (Oliver *et al.*, 2003). Current findings on calves infected with the GIII.2 bovine norovirus found moderately severe weakness followed by acute but persistent diarrhoea (Jung *et al.*, 2014). Viral RNA was detected in serum for up to 5 days after infection, indicating viraemia, while RNA was detected in faeces for up to 20 days, indicating viraemia (Karst *et al.*, 2014). Despite a significant antibody response, long-term viral RNA excretion may play a role in the persistence of bovine noroviruses in cattle. From 12 hours to 4 days following infection, newborn calves infected with the Jena virus, a GIII.1 bovine norovirus, showed diarrhoea and significant symptoms of gut pathology, such as severe villous atrophy (Otto *et al.*, 2011). Noroviruses, which cause long-term subclinical chronic infections of the

intestine in wild-type mice, are now recognised as prevalent pathogens in laboratory mice (Arias *et al.*, 2012). Noroviruses have been identified in both field mice (Apodemus agrarius) and wood mice (Apodemus sylvaticus) (Smith *et al.,* 2012).

In Japan, the United States, and Europe, noroviruses have been identified from pigs (Wang *et al.*, 2005). When gnotobiotic piglets are infected with GII porcine noroviruses, they usually develop moderate self-resolving diarrhoea (Karst *et al.*, 2014). Due to the structure of the pig intestine being similar to human that of people, gnotobiotic piglets can easily be infected with particular genogroup II human noroviruses, making them a good experimental model system (Cheetham *et al.*, 2006). When gnotobiotic pigs are infected with a GII.4 human norovirus, most of the animals have mild diarrhoea, faecal discharge, and antibody response. The symptomatic aspect of infection is especially important in the testing of prospective medicines and vaccines, where disease prevention is the most important criterion (Karst *et al.*, 2014). In reality, this model has also been used to show the effectiveness of a number of human norovirus vaccine candidates (Kocher *et al.*, 2014) as well as a number of treatments (Bui *et al.*, 2013). The discovery that canine noroviruses have the same cellular receptors as human noroviruses indicates that animal noroviruses might potentially be transmitted to humans (Caddy *et al.*, 2014).

3.4 Norovirus Transmission

Norovirus can be transmitted to someone else by close contact with an infected individual, eating infected food or drinking contaminated drinks, contacting items with

norovirus on them and then placing contaminated fingers in mouth, sharing utensils or glasses with people who are ill with norovirus can spread the infection to others (Centers for Disease Control, 2015). There seem to be no controlled outbreak studies in which both animals and people were sampled at the same time. A diseased dog was epidemiologically connected to a calicivirus outbreak in a nursing home in the United Kingdom in 1983 (Villabruna *et al.*, 2019). Faeces of animals that contain norovirus will flow into rivers and contaminate water sources. During the years 2002–2003, human NoV GII-group strains were found in river water in Korea, where pig farming businesses are widely developed in surrounding cities (Keum *et al.*, 2009). In short, ingestion of contaminated food or water, either through the faecal-oral route or through airborne particles and contact with infected surfaces, transmits NoVs (Cavicchio *et al.*, 2020).

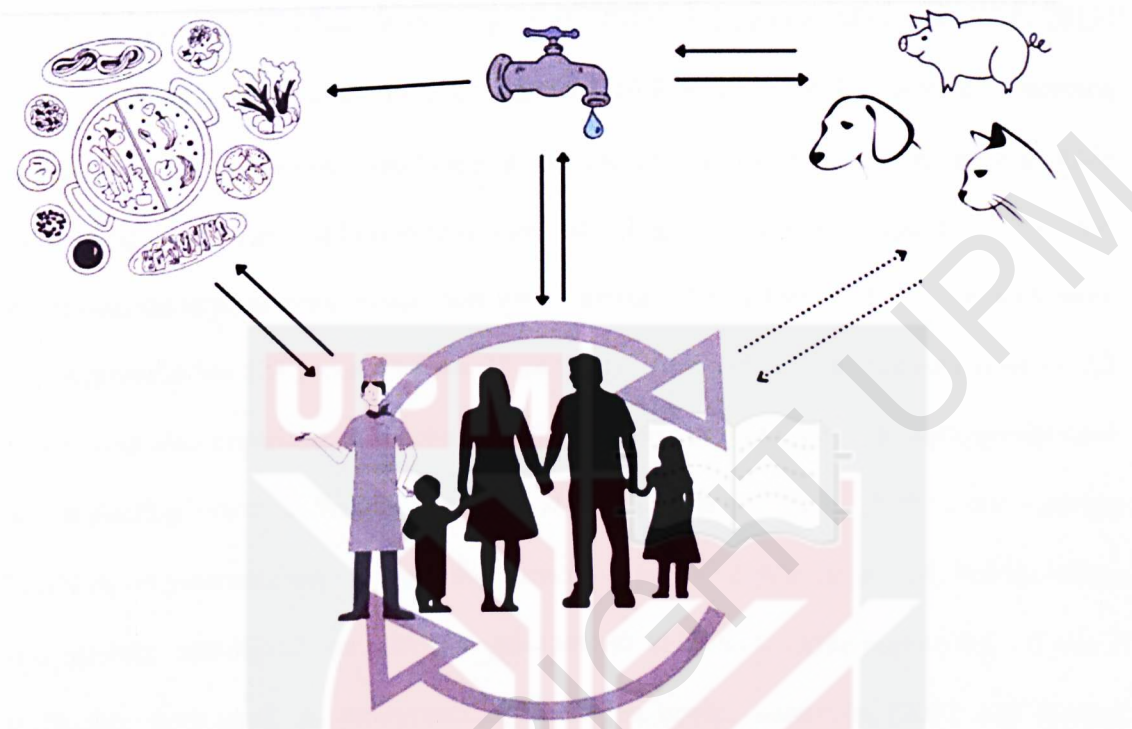


Figure 3: Transmission cycle of norovirus. Norovirus can be transmitted in humans by close contact with an infected individual, eating infected food or drinking contaminated water. Faeces of animals that contain norovirus will flow into rivers and contaminate water sources. Studies suggesting human to animal norovirus transmission and vice versa are not confirmative enough.

3.4.1 Animal-to-human Norovirus Transmission

Regarding animal-to-human transmission, although no animal norovirus has been found in human faeces, there is some serological data that suggests there is possible animal-to-human transfer (Villabruna *et al.*, 2019). There have been a few investigations that have

found seroprevalence of bovine (Menon *et al.*, 2013) and canine (Mesquita *et al.*, 2013) norovirus in humans. Antibody titres against GIII.2 VLPs from 210 bovine or porcine veterinary experts were evaluated to age, gender, and residency matched controls in a Dutch study to see if more animal exposure is mirrored in higher titers against animal noroviruses. In comparison to the control group, more veterinarians exhibited anti-GIII.2 immunoglobulin G (IgG) antibodies (28 percent versus 20 percent). Antibodies to canine norovirus GVI.2 VLPs were also examined in a cohort of 373 veterinarians compared to age, gender, and region matched controls (Widdowson *et al.*, 2005). Compared to 5.8% in the control group, 22.3% of veterinarians were seropositive for norovirus GVI.2 (Mesquita *et al.*, 2013). When convalescent anti-GIII.2 sera from a gnotobiotic calf or specific anti-GIII.2 or GII.3 antibodies were used, no cross-reactivity between bovine norovirus GIII.2 and human norovirus GI.3, GII.1, GII.3, GII.4, GII.6 was identified (Vildevall *et al.*, 2010). In an age-strengthened cohort of 535 people in Italy, however, cross-reactivity was detected between the more strongly related human GIV.1 and canine GIV.2 noroviruses, with 28.2 percent of the sera reacting to both GIV.1 and GIV.2 VLPs and just 0.9 percent detecting exclusively GIV.2 VLPs. In short, human serum samples taken in Italy are positive towards Genogroup IV norovirus specific antibodies (Di Martino *et al.*, 2014).

3.4.2 Human-to-animal Norovirus Transmission

In relation to human-to-animal transmission, several researchers have looked into the likelihood of human norovirus transmission to animals by testing animal faecal samples for human noroviruses or looking into seroprevalence against different human norovirus strains.

One case-control study including 92 dogs from Finnish households came the closest to an outbreak (Villabruna *et al.*, 2019). The main determinant for inclusion was that the dog or a human in the family had vomited or had diarrhoea (Summa *et al.*, 2012). Four dogs tested positive for PCR, and they all originated from homes where at least two individuals had serious gastroenteritis symptoms that had gone away within three days of the dog samples being taken. Two GII.4 variations and one GII.12 genotype were defined based on a 370-nt area, one of which was similar to the virus detected in the owner's faeces (Villabruna *et al.*, 2019). In two dog populations, the studies were done to look at the seroprevalence of human noroviruses (GI.1, GI.2, GI.3, GII.3, GII.4, GII.6, and GII.12). In 1999–2001, sera were taken from dogs in a rehoming kennel, and in 2012–2013, sera were gathered from a diagnostic laboratory. All in all, seropositivity against GI was quite low, however 10.7–18.6% were positive for GII VLPs (Caddy *et al.*, 2015). These findings imply that human noroviruses may infect dogs, while more research is needed to determine potential cross-reactivity with non-human viruses such as GVI.2 (Di. Martino *et al.*, 2017).

Human norovirus was found in pig faeces in several studies, and two of them found more than one genotype. The intestinal material of 20 apparently healthy 6-month-old pigs was examined monthly with calicivirus-specific primers in a longitudinal investigation in Japan. 3.1% (11/354) of these tested positive for human GII, with no discernible seasonal pattern (Nakamura *et al.,* 2010). These isolates were categorised as GII.4, GII.3, and one GII.13 based on incomplete capsid sequences, all three genotypes that had been described in human epidemics during that season (Villabruna *et al.*, 2019). In another research, 7 percent

of 530 faecal samples from asymptomatic pigs (less than 8 months) from six farms in Taiwan screened positive with RdRp-specific primers, whereas 32 percent tested positive with GII capsid-specific primers, 41 percent in winter and 26 percent in summer (Chao *et al.*, 2012). Pigs of all ages and from various farms were found to have the norovirus GII.4 and GII.2 classified sequences (Nakamura *et al.,* 2010).

Human norovirus antibodies have been found in healthy domestic pigs in Nicaragua and the United States, with prevalences ranging from 52 to 70 percent. Despite the fact that the antibodies recognised VLPs from GI.1, GII.1, GII.3, and GII.4, they were unable to prevent them from adhering to pig mucin (Bucardo *et al.*, 2016). GII.17 was the most common human norovirus genotype in certain Asian nations during the 2014–2015 pandemic season (Chan *et al.*, 2017). The GII.7 sequences were 99–100% similar to one another, with a human norovirus sequence being 95% identical (KJ196295) (Villabruna *et al.*, 2019). Antibodies against multiple human norovirus genotypes were also found in captive primates in the United States; IgG against GI.1, GII.4, GII.5, and GII.7 VLPs was found in mangabeys (85%), macaques (around 60–65%), and chimps (92%) (Farkas *et al.,* 2010).

3.5 Norovirus Detection Methods

Faecal, intestinal contents and serum samples are types of samples from animals for animal norovirus detection. Faecal and intestinal content are used in molecular detection while serum is used in serology detection (Caddy *et al.*, 2013). Methods of norovirus

detection which include RT-PCR, southern blot (van Der Poel *et al.*, 2000), real time RT-PCR (Machnows *et al.*, 2014) and ELISA (Di Martino *et al.*, 2010).

3.5.1 Norovirus Detection through PCR

RT-PCR is to amplify larger genome fragments suitable for sequence analysis by using primer (Erlich *et al.*, 1991). Real time RT-PCR allows for the detection of PCR amplification through graphs of amplicons and more towards quantitative. Real time RT-PCR monitor fluorescence signals (Nakamura *et al.*, 2010). Southern blot is used to detect specific DNA molecules reported in only one paper (van Der Poel *et al.*, 2000). Among the test methods, RT-PCR is the most common method that is used based on the number of publication reviewed (Figure 2).

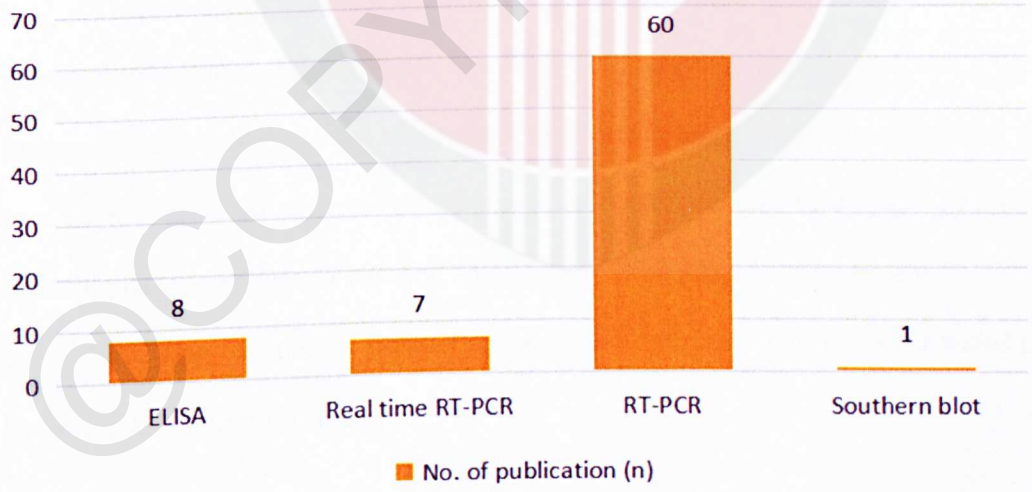


Figure 4: RT-PCR is the most common method used for animal norovirus detection based on number of publications followed by ELISA, real time RT-PCR and southern blotting

Phosphate-buffered solution was added to stool samples to a final concentration of 10% (mass/volume). The materials were vortexed briefly before being centrifuged at 12,000 rpm for 1 minute and the supernatant was collected. The QIAamp Viral RNA Kit was used to extract RNA from faecal samples (QIAGEN, Hilden, Germany) (Ahmed *et al.*, 2020). Reverse transcription (RT)–PCR was used to identify norovirus by amplifying the capsid gene at the C region (Kittigul *et al.*, 2010). The partial capsid genes of GI and GII noroviruses have amplicons size of 330 and 344 bp, respectively (Ahmed *et al.*, 2020). RT-PCR was used to amplify the RNA-dependent RNA polymerase (RdRp) gene (Saito *et al.*, 1998). The partial RdRp gene has a 470-bp amplicon size (Ahmed *et al.*, 2020). All of the samples were taken from pigs who had no signs or symptoms of gastroenteritis (Chao *et al.*, 2012).

There are two types of primers for RT-PCR which include the commonly used universal calicivirus primers (P290 and P289). 2 sets of primers which are reverse and forward primers target a partial sequence of the RdRp to amplify base pair fragment. Species specific primers used such as the porcine specific primers are PNV7 and PNV8, canine specific primers include JV102 and JV103 and feline specific primers are FNoV-F9 and FNoV-R15. Species specific primers are used for confirmatory results after tested positive by universal calicivirus primers.

Primer/Probe	Sequence 5'- 3'	References
P290	GATTACTCCAAGTGGGACTCCAC	Jiang *et al.* (1999)
P289	TGACAATGTAATCATCACCATA	Jiang *et al.* (1999)
JV102	TGG GAT TCA ACA CAG CAG AG	Mesquita *et al.* (2010)
JV103	TGC GCA ATA GAG TTG ACC TG	Mesquita *et al.* (2010)
PNV7	AGGTGGTGGCCGAGGAYCTCCT	Wang *et al.* (2006)
PNV8	TCACCATAGAAGGARAAGCA	Wang *et al.* (2006)
FNoV-F9	GCCCACTGGATWTACACCCTCTC	Castro *et al.* (2015)
FNoV-R15	CTGATGGTTGGGTCCTCTGGTCCA	Castro et al. (2015)

Table 2: Published norovirus primers and their targeted DNA region in animal norovirus

3.5.2 Norovirus Detection through ELISA

Detection of norovirus can be through ELISA by using serum samples. Virus-like particles (VLP) act as antigen. Specific antibodies will bind to antigen. Norovirus specific

IgG antibodies can be detected n sera through ELISA. Around 500 canine serum samples from private veterinary clinics in 14 countries of Europe. The samples were collected from September 2009 until January 2010. Sf9 insect cells were used to create virus-like particles (VLP) by infecting it with a recombinant baculovirus. These VLP are encoding for the full length of the genome of canine norovirus strain Ca/PT/2007/GVI.2/Viseu st the region of ORF 2 and ORF 3 (VP1 or VP2). The VLPs' purity was confirmed using Coomassie blue-stained SDS-PAGE gels, and the VLPs' structure and sizes were confirmed using electron microscopy. All dog sera were tested for IgG antibodies against canine norovirus (GVI.2) using an in-house VLP-based ELISA. A serum sample was considered positive when the corrected OD value (VLP-coated wells minus non-coated wells) was greater than the mean of the uncoated wells plus 3 standard deviations (Mesquita *et al.*, 2014).

3.6 Worldwide Distribution of Animal Norovirus

Figure 5: The world map demonstrates the distribution of animal norovirus. Green shaded show countries that have reported animal norovirus. Yellow, red and purple boxes represent cat, dog and pig, respectively.

Figure 6: Distribution of animal norovirus in the Americas where norovirus of pigs, dogs and cats are detected.

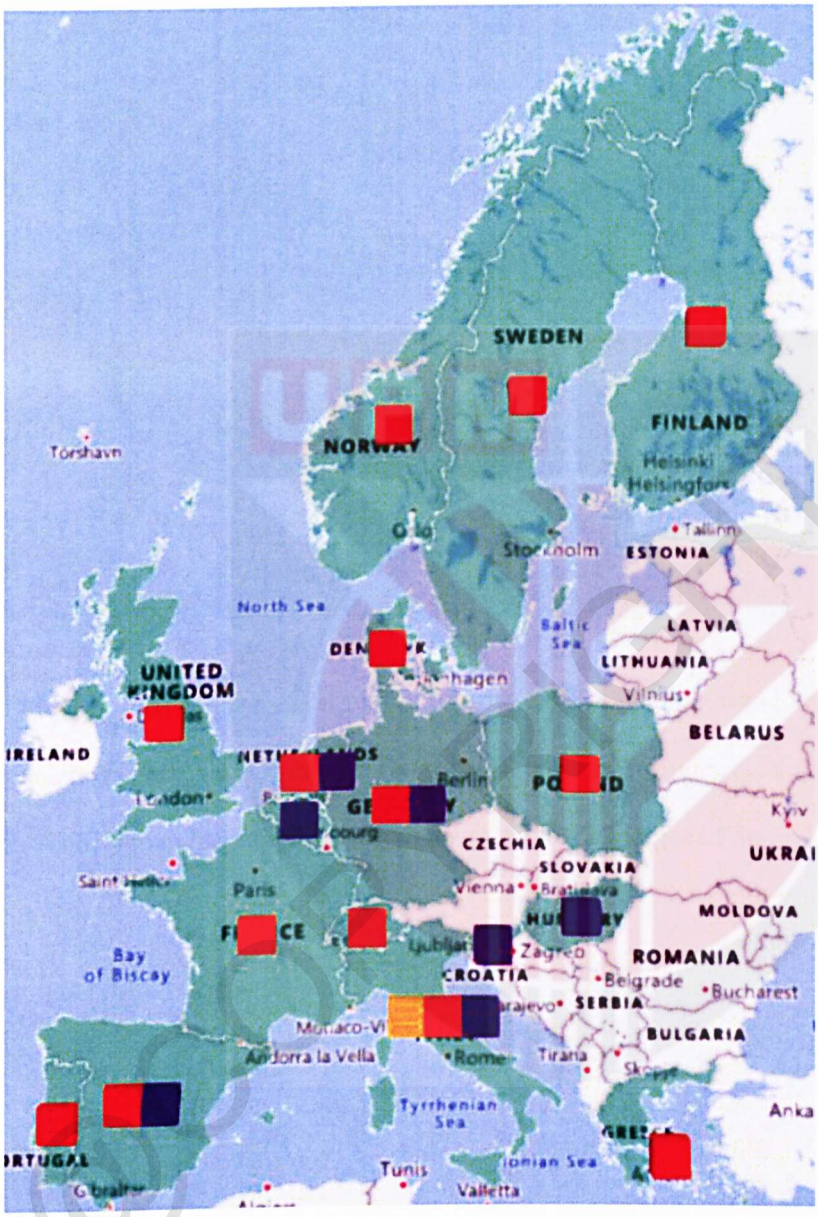


Figure 7: Distribution of animal norovirus in Europe where animal noroviruses are detected in cats, pigs and felines. Canine norovirus is detected in almost the whole of Europe.

Figure 8: Distribution of animal norovirus in Asia where animal noroviruses are detected in pigs, dogs and cats. Of these three species, porcine norovirus is the most commonly detected in Asia. Japan has reported norovirus in all the 3 species of animals.

Figure 9: Distribution of animal norovirus in Oceania where only New Zealand reported porcine norovirus. Feline or canine norovirus is not reported.

3.6.1 Distribution of Animal Norovirus in Malaysia

In Malaysia, norovirus is detected in humans only, where animal norovirus is yet to be reported. In humans, a survey was carried out during an outbreak of diarrhoea in a kindergarten in Sabah, Malaysia. Stool samples from teachers and children were tested for rotavirus and norovirus using an ELISA and RT-PCR. Norovirus genotype GII.2 was found in all of the samples (Ahmad *et al.*, 2020).

Previous study on molecular detection of norovirus in healthy pigs, dogs and cats in peninsular Malaysia shows negative. The failure to find NoVs in faeces samples could be attributable to sampling of healthy animals, where NoV shedding in faeces lasts just 5 days during acute infection or perhaps the animals have not been exposed before to norovirus infection (Tan *et al.*, 2020).

CONCLUSION

This review suggests that norovirus is ubiquitous where animals and humans worldwide which include Asia, Europe and the Americas could be infected. Secondly, norovirus is transmitted through the faecal-oral route. In addition, animals and humans that are infected with norovirus will show similar symptoms. Most would experience gastroenteritis which include vomiting and diarrhoea. Fourth, diagnosis of norovirus infection in animals can be done through molecular and serology detection. Most common method is through RT-PCR. Most studies use the approach to detect norovirus antigen rather than antibody. Next, human norovirus has been detected in Malaysia but animal norovirus is yet to be detected. Recent study on detection of animal norovirus antigen on healthy animals' population was negative although several reports showed that norovirus could be detected in symptomatic or asymptomatic and juvenile or adult animals. Lastly, of all 18 countries surveyed, few countries like Italy, Japan and USA are able to detect norovirus antigen in pigs, dogs and cats.

RECOMMENDATIONS

In preparation for possible outbreak of norovirus infection in animals, target surveillance should be done for detecting trans-species transmission. When there are cases of human norovirus infection, at the same time, an initiative should be made to do surveillance on animals nearby to detect spillover to animals.

Since human norovirus antigen and antibody are detected in Malaysia and the possible transmission of human to animal has been reported, perhaps future studies should investigate the presence of antibodies in the animal population to detect any past exposure to norovirus. The aim of seroprevalence research is to detect post-exposure of animals to the virus in order to verify the animals' lifetime exposure to the virus.

In addition to that, future studies should also target the clinically ill animal populations, especially those animals with gastroenteritis symptoms. Animals with diarrhoea symptoms would be in the active infection stage and likely to shed the antigen to the environment and serve as a source of infection to other naive animals.

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APPENDICES

Appendix 1

Detection of animal norovirus in cats, dogs and pigs by various diagnostic test methods in different countries

Faecal samples are analysed by reverse-transcription-polymerase chain reaction (RT-PCR), real-time RT-PCR or EM and serological studies.

G2SKF/G2SKR (GII, capsid), MON432/MON477 (norovirus)

Adults in pigs are more than 6 months old and finishers.

Virus-like particles (VLPs)

Animal norovirus

Country	Patient Species	Genotype	Prevalence (%)	Detection method	Primers, probes and antigens used	Samples F=Faeces S=Sera IC= Intestinal content	Age/ Clinical status A=Adult J=Juvenile +=Symptomatic -= Asymptomatic	Reference
Asia								
China	Pigs	GII	2/904 (0.2)	RT-PCR	p280, p290	F	J/A-	Shen *et al.* (2009)
	Pigs	None	0/209 (0)	RT-PCR	primers were used to detect human and porcine caliciviruses	F	J/A -	Shen *et al.* (2011)

	Pigs	novel genotype in the GII group, GII.11	2/12 (16.7)	RT-PCR	NA different primer sets for the detection of PoNoV	F	J+	Shen *et al.* (2012)
	Dogs	GVII	2/NA (NA)	RT-PCR	NA	Rectal swab	NA	Tse *et al.* (2012)
	Dogs	GVI.1, GIV.2, GVI.2 strain Dog/M9/18/CH	21/268 (7.8)	RT-PCR	(MK067295) position 4742–5172 bp fragment of GVI.2/AN1640/2017/USA	F	+	Ma *et al.* (2021)
Korea	Dogs	GIV.2	14/459 (3.1)	RT-PCR	JV102 & JV103	F	+/-	Lyoo *et al.* (2018)
			68/427 (15.9)	ELISA	P-domain of GQ443611	S		
	Pigs	GII.21	3/567 (0.53)	RT-PCR	NORO-DG35 OF, NORO-DG35 IF	F	NA	Song *et al.* (2011)
	Pigs	GII.11, GII.18	10/537 (1.7)	semi-nested RT-PCR	GIIF1, GIIR, GIIF2	F	J/A +/-	Keum *et al.* (2009)
	Pigs	none	0/296(0)	RT-PCR/ nested-PCR	NA	F	J/A	Lyoo *et al.* (2020)

Japan	Dogs	GIV.2	2/97 (2.1)	RT-PCR	p290d-p289d	F	+	Soma *et al.* (2015)
	Cats		1/83 (1.2)					
	Cats	GIV.2	1/NA (NA)	RT-PCR	p290d, p289d	Rectal Swab	NA	Takano *et al.* (2015)
	Pigs	GII	4/1117 (0.4)	RT-PCR, nested PCR	human SRSV, 35/36, NV81/NV82, SMA82	IC	-	Sugieda *et al.* (1998)
	Pigs	GII	1/24 (4.2)	RT-PCR	p290/289	IC	J+/-	Yin *et al.* (2006)
	Pigs	GII.11, GII.18, GII.19	55/354 (15.5)	RT-PCR, Real time RCR	p290, p280, G1SKF, G1SKR, G2SKF, G2SKR Real time PCR: COG2F, ALPF, and COG2R	F, IC	A-	Nakamura *et al.* (2010)
	Pigs	GII	95/266 (36)	enzyme immunoassay (EIA)	VLP of SW918 from genogroup II NV	S	J	Farkas *et al.* (2005)
	Pigs	NA	11/190 (5.8)	RT-PCR	NA	F	-	Okada *et al.* (2019)
Taiwan	Pigs	GII.11	9/533(1.7)	RT-PCR	p290 and p110, NV2oF2/NV2oR, G2F3/G2SKR	F	J/A -	Chao *et al.*, 2012
Oceania								

New Zealand	Pigs	G I-III	2/23 (8.7)	conventional RT-PCR	J4549f, J5041r, J4972f, J5468r, J5411f, J5988r, J5938f, J6648r	F	J-	Wolf *et al.*, 2009
Europe								
Italy	Dogs	GIV.2	1/1 (100)	RT-PCR	p289/p290	F	J+	Martella *et al.* (2008)
	Dogs	GIV.2	4/183 (2.2%)	RT-PCR	p289-p290 JV12Y-JV13I	F	J+	Martella *et al.* (2009)
	Dogs	GVI.2	6/10 (60)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 & ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
	Dogs	GVI.2	11/239 (4.6)	RT-PCR	p289-p290, JV12Y–JV13I	F	J+/-	Bodnar *et al.* (2017)
	Dogs	GIV.2	5/103 (4.8)	ELISA	VLPs were developed with the RNA of the prototype lion NoV GIV strain Pistoia/387/06/ITA	S	A	Di Martino *et al.* (2010)
	Dogs	GIV.2 & GVI.2	66/516 (12.8)	ELISA	GIV.2 and GVI.2 VLPs	S	J/A	Di Martino *et al.* (2017)

		GIV.2	20/516 (3.9)					
		GVI.2	46/516 (8.9)					
	Pigs	GII.11	1/201(0.5)	RT-PCR	p290-p289, p290-p110, PNV7-PNV8	F	J/A -	Di Bartolo *et al.* (2014)
		None	0/89 (0)				J +	
	Pigs	GII.11, GII.18, GII.19	0/242 (0)	RT-PCR	PNV7-PNV8	F	J/A +/-	Monini *et al.* (2015)
	Pigs	GII.P11, GII.P18	29/225 (11.4)	RT-PCR	p290-p110	F	J/A	Cavicchio *et al.* (2020)
	Pigs	GII.P11	2/79(2.53)	RT-PCR	NVG4F and VN3T20	F	J/A	Laconi *et al.* (2020)
	Cats	GIV.2	3/105 (2.9)	RT-PCR	p289–p290, JV12Y–JV13I	F	J +/-	Di Martino *et al.* (2016)
	Cats	GIV.2	34/211 (16.1)	ELISA	VLPs were developed with the RNA of the prototype lion NoV GIV strain Pistoia/387/06/ITA	S	A	Di Martino *et al.* (2010)
Spain	Dogs	GVI.2	2/26 (7.7)	RT-PCR	p289-p290, JV12Y–JV13I	F	J+/-	Bodnar *et al.* (2017)

	Pigs	NA	27/221 (12)	RT-PCR, real-time RT–PCR	p289/p290, JV12/JV13. qRT-PCR: probes (GI or GII)	F	J/A +/-	Halaihel *et al.* (2010)
Greece	Dogs	GIV.2	6/72 (8.3)	RT-PCR	p289-p290, JV12Y & JV13I	F	J+	Ntafis *et al.* (2010)
Portugal	Dogs	GVI.1	29/105 (27.6)	RT-PCR	JV102 & JV 103 p289-p290	F	+/-	Mesquita *et al.* (2010)
	Dogs	GIV.2	7/7 (100)	RT-PCR	JV102 & JV103	F	J+	Mesquita *et al.* (2012)
	Dogs	GIV.2	60/256 (23)	RT-PCR	JV102 & JV103	F	+/-	Mesquita & Nascimento (2012)
	Dogs	GVI.2	64/100 (64)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 & ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
Hungary	Dogs	GVI.2	2/63 (3)	RT-PCR	p290/p289	F	NA	Mihalov-Kovács *et al.* (2014) Villabruna *et al.* (2019)

	Dogs	GVI.2	0/10 (0)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 & ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
	Pigs	GII	1/17 (5.9)	RT-PCR	p289/p290	F	J/A +/-	Reuter *et al.* (2007)
German y	Dogs	none	0/3 (0)	RT-PCR	p289-p290, JV12Y–JV13I	F	J+/-	Bodnar *et al.* (2017)
	Dogs	GVI.2	8/50 (16)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing the full length VP1/VP2 (ORF2 & ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
	Pigs	GII.18	17/120 (14.2)	real-time RT-PCR	Mon 431, Mon 432, Mon 433, Mon 434	F	A	Machnows *et al.* (2014)
France	Dogs	none	0/26 (7.6)	RT-PCR	p289-p290, JV12Y–JV13I	F	J+/-	Bodnar *et al.* (2017)
	Dogs	GVI.2	10/50 (20)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with	S	J/A	Mesquita et al. (2014)

					recombinant baculovirus containing full length VP1/VP2 (ORF2 & ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu			
Netherlands	Pigs	GII	2/100 (2)	RT-PCR, Southern blot	JV12, JV13	F (pooled)	A	van Der Poel *et al.* (2000)
	Dogs	GVI.2	17/50 (34)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 and ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
Belgium	Pigs	GII.19	2/43 (4.7)	RT-PCR	JV12-13, p289–290, swNo F/R	F	J/A +/-	Mauroy *et al.* (2008)
Slovenia	Pigs	GII.11 GII.18	5/406 (1.2)	RT-PCR	JV12Y/JV13I, p290/NVp110, JV12Y/NVp110, SR80/JV33, G1SKF/R and G2SKF/R	F	J/A -	Mijovski *et al.* (2010)
UK	Dogs	None	0/228	Real-time RT-PCR	primer-probe set used for GIV & GVI	F	A +/-	Caddy *et al.* (2013)
		Total	189/396 (47.7)	ELISA	VLPs of GIV.2 (EU224456.1), GVI	S	J/A	

		GIV.2	47/396 (11.9)		(GQ443611.1), GVI.1 (FJ692501.1)			
		GVI	8/396 (2.0)					
		GVI.1	78/396 (19.7)					
	Dogs	GVI.2	23/56 (46)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 and ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
	Dogs	GIV.2, GVI.1, GVI	0/248	Real time RT-PCR	primer-probe set designed to identify six different strains of canine norovirus (CNV)	F	A +/-	Caddy *et al.* (2015)
			147/325 (45.2)	ELISA	pooled CNV VLPs	S	NA	
Ireland	Dogs	GVI.2	0/10 (0)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 and ORF3 of genome) of canine	S	J/A	Mesquita *et al.* (2014)

					norovirus strain Ca/PT/2007/GVI.2/Viseu			
	Pigs	None	0/292 (0)	RT-PCR	p289/p290	F	J-	Collins *et al.* (2009)
Poland	Dogs	GVI.2	16/50 (32)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 and ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
Finland	Dogs	GVI.2	7/10 (70)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 and ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
	Dogs	GI, GII, and GIV	0/92 (0)	real-time RT-PCR	COG2R/QNIF2 and QNIFS for GII14 and Mon4F/Mon4R and Ring4 for GIV NoVs. In-house primer and probe combination QNIF416/QNIF3	F	J/A +/-	Summa *et al.* (2012)

					and JJV1P17 was used in GI analysis.			
Norway	Dogs	GVI.2	16/50 (32)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 and ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
Sweden	Dogs	GVI.2	4/10 (40)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 and ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
Denmark	Dogs	GVI.2	10/50(20)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected with recombinant baculovirus containing full length VP1/VP2 (ORF2 and ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu	S	J/A	Mesquita *et al.* (2014)
Switzerland	Dogs	GVI.2	2/10 (20)	enzyme immunoassay (EIA)	VLPs were produced in Sf9 insect cells infected	S	J/A	Mesquita *et al.* (2014)

					with recombinant baculovirus containing full length VP1/VP2 (ORF2 and ORF3 of genome) of canine norovirus strain Ca/PT/2007/GVI.2/Viseu			
The Americas								
USA	Dogs	GIV.2, GVI.1 & GVI.2	46/213 (21.6)	RT-PCR	Tx30SXN, JV12Y & JV13I	F	+	Ford-Siltz *et al.* (2019)
	Pigs	GII	78/110 (71)	enzyme immunoassay (EIA)	VLP of SW918 from genogroup II NV	S	A	Farkas *et al.* (2005)
			0/104 (0)	RT-PCR	p289H,I-p290H,I,J,K	F/IC	J/A +/-	
	Pigs	GII.11, GII.18, GII.19	6/275 (2.2)	RT-PCR	p290/110	F	A-	Wang et al. (2005)
	Pigs	GII.11, GII.18, GII.19	64/621 (10)	RT-PCR, microwell hybridization	PNV7& PNV8	F	J/A +/-	Wang et al. (2006)
	Pigs	GII.11, GII.18	78/413 (11.6)	RT-PCR, microwell hybridization assay	PNV7 and PNV8, p290 and p110, G2SKF and G2SKR,	F(Pooled)	A-	Scheuer *et al.* (2013)

					-mixture of three probes (PoNoroP1A, PoNoroP1B, and PoNoroP1C) to detect all three genotypes (GII.11, -18, and -19) of porcine NoVs			
	Pigs	GII.18	0/139	RT-PCR	p290, P110, JV12Y, JV13I	F	J	Sisay *et al.* (2013)
	Cats	GIV.2	6/24 (25)	RT-PCR	p290/289, FNoV-F9 and FNoV-R15	F	J/A+	Pinto *et al.* (2012)
	Cats	Feline norovirus	1/6(16.7)	RT-PCR, nested PCR	viral metagenomics, random hexamer primer	(Pool) F	-	Zhang *et al.* (2014)
Brazil	Pigs	GII. 11, 18 and 19	20/261(8)	RT-PCR	p289/289HI and p290/290HIJK Cap C, Cap D3, Cap D1	F/IC	J/A +/-	Cunha *et al.* (2010)
	Pigs	GII.18	1/96 (1)	RT-PCR	p289/289HI, p290/290HIJK, Mon431 and 432, Mon433 and 434	F	J/A +/-	Cunha *et al.* (2010)
	Pigs	None	0/169 (0)	RT-PCR	p289/p290, p289/289HI, p290/290HIJK	F	J +/-	das Merces Hernandez *et al.* (2014)
	Pigs	GII.11	58/112 (51.8)	RT-PCR	SwNV1, SwNV2	F	A-	Silva *et al.* (2015)

	Pigs	NA	2/30 (6.7)	RT-PCR	NA	F	J+	Almeida *et al.* (2018)
	Cats	GIV	1/29(3.4)	RT-PCR, real-time RT-PCR	p289H/p290H, FNoV-F9, FNoV-R1, Mon 4F, Mon 4R, probe Ring 4	F	J+	Castro *et al.* (2015)
Canada	Pigs	GII.18 GII.11	26/120 (22.7)	RT-PCR	Monroe region B primers or Ando region A primers	F	NA	Mattison *et al.* (2007)
	Pigs	Swine norovirus	4/200 (2)	RT-PCR, real time RT-PCR	p289/P290 real time RT-PCR:COG2F and COG2R and probe RING2	F	NA	L'Homme *et al.* (2009)
	Pigs	GII.11/18	17/20 (85)	RT-PCR	p289/p290, p289N/p290N	Pooled F/F	J/A	L`Homme *et al.* (2009)
			12/66 (18)			IC	A-	Villabruna *et al.* (2019)
Venezuelan	Pigs	GI, GII	0/204 (0)	RT-PCR	289/290, GLPSG1/ YGDD1, and GLPSG2/YGDD1	F	J +/-	Martínez *et al.* (2006)
Nicaragua	Pigs	GII.4/Dijon	96/137 (70)	ELISA	VLPs belonged to NoV of GII.4 genotype and were derived from the strains 'HS194'	S	J/A-	Bucardo *et al.* (2016)
		GII.4/ HS194	94/137 (69)					

		GII.3/Khron1	80/137 (58)					
Africa								
South Africa	Pigs	none	0/120	RT-PCR	p289/p290	Rectal swab	J	Taku *et al.* (2017)
Ethiopia	Pigs	none	0/117	RT-PCR	G2SKF/G2SKR, p290/p110	F	J/A +/-	Sisay *et al.* (2016)