EPIDEMIOLOGICAL IMPACT OF SWINE ZOONOTIC DIGESTIVE VIRUSES – REVIEW

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Abstract

Infectious diarrhea of farm pigs causes some of the most significant financial losses for producers working in the pork industry through the loss of efficiency, as well as the loss of overall profitability of production. Highly virulent diseases, such as porcine epidemic diarrhoea, result in very high piglet mortality, causing producers enormous financial difficulties. Recurrent and less endemic diseases however, have greater long-term overall effects on health and productivity. The prevalence of swine diarrhea can vary from country to country, from one farming system to another and even from one farm to another.

The increasing pressure of pig production, the wide network of imports-exports, the constant evolution of pathogens that allow them to develop new adaptation and diversification mechanisms, and climate change, are some of the challenges faced by the global pork industry. Thinking about viruses being transmitted across species implies taking into consideration all issues arising from these pathogens. They not only reveal the vulnerabilities in human societies, whose functioning is disrupted by these outbreaks, but also the fragilities of the environments in which they appear.

Key words: swine, astrovirus, rotavirus, norovirus, hepatitis E virus

Etiologic investigations of infectious diarrhea in swine were long limited to bacteria and protozoa. The advent of electron microscopy and molecular biology showed that diarrhea could also be caused by viruses, both in humans and in other animals. Several pathogens have been intensively studied, while others have yet to be investigated even though they have been reported in pigs all around the world. Recent events have shown the importance of the zoonotic potential of viruses, for example directly but also via potentially infected or contaminated food. The emergence of pathogens through inter-species passage corresponds to rare events, but a very high mutation rate increases their probability occurrence as evidenced by the over-representation of single-stranded RNA viruses among the known examples of species jumping.

Although the molecular mechanisms necessary to cross the species barrier are very diverse, the presence of compatible cell receptors represents a crucial step and several examples of crossing the species barrier have shown the determining role of mutations allowing viruses to recognize their receptor on cells of the new species target. Under these conditions, the risk of inter-species transmission will be higher that the receptors are phylogenetically conserved. This review evaluates the impact of porcine astroviruses, rotavirus, norovirus and hepatitis E virus in pig production network.

Porcine astrovirus (PAstV) has been poorly studied and has been associated mainly with gastroenteritis. Astroviruses are naked single-stranded RNA viruses, small in size (28 to 30 nm) belonging to the *Astroviridae* family. Astroviruses have a genome composed of 3 ORFs designated ORF1a, ORF1b and ORF2. ORF1a and ORF1b encode for non-structural polyproteins, including a protease and an RdRp. ORF2 encodes for the capsid structural protein transcribed by a subgenomic mRNA. The great diversity of *Astrovirus* species has led to multiple efforts to classify these different genera and species. This great genetic diversity makes it possible to find astroviruses in several animals in addition to humans, including cats, dogs, cattle, mice, deer, pigs, sheep, mink, bats, cheetahs, rats, rabbits and

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other marine mammals, as well as in chickens, turkeys, ducks, pigeons and guinea fowl. Based on genetic analysis of the complete capsid region at the amino acid level, mammalian astroviruses will be divided into two main genogroups: genogroup I and genogroup II. Each genogroup includes astroviruses infecting different host species, and can be further subdivided based on both genetic and host species criteria (Rawal G, Linhares DC, 2022)

In pigs, five different groups of porcine astroviruses have been identified (porcine astrovirus groups 1-5), these differences being due to their large genomic disparities. However, only porcine astrovirus "1" is part of *Mamastrovirus*.

Genotypes A and B are able to infect humans (Carter, 2005). Among the viral agents known to cause enteric disease, importance of astroviruses as a cause of foodborne disease is perhaps the less well characterized (Percival et al., 2004). In infected people, the disease seems similar to that caused by rotaviruses, although it is much less severe (diarrhea of 2 3 days that does not cause significant dehydration). Other symptoms include headache, malaise, nausea, vomiting, and mild fever (Percival et al., 2004; Méndez and Arias, 2007).

Astroviruses can be transmitted through food, water, contaminated materials and person-to-person contact (Bosch et al., 2014). Astroviruses are remarkably resilient in the environments. They resist several treatments including chlorinated water (7-9), low pH, lipid solvents and ionic detergents and non-ionic (Maclachlan et al, 2016). Molecular analysis has revealed the close relationship of PAstV with astroviruses of humans (HAstV) and cats (FAstV).

Astroviruses appear to be ubiquitous in young animals and often associated with self-limiting gastroenteritis. Extra-intestinal infections have also been observed, causing encephalitis in cattle (Li et al., 2013), pigs (Arruda et al, 2017; Matias et al, 2019; Rawal, 2019) and mink (Blomström et al, 2010). Porcine astroviruses were detected almost everywhere around the world, including Greece (Stamelou et al, 2022), Hungary (Boros et al, 2017), Czech Republic (Indik et al, 2006), US (Rawal, Matias et al, 2019), Canada (Laurin et al, 2011; Luo et al, 2011) (Table 1).

Table 1.

Epidemiology of swine astrovirus based on molecular detection studies

Sample type	Overall detection	Country	Authors
Faecal samples	80%	Canada	Luo et al, 2011
Faecal samples	23,8%	Colombia	Ullua et Gutierrez, 2010
Faecal samples	61,33%	US	Mor et al, 2012
Faecal samples	34,25%	Czech Republic	Dufkova et al, 2013
Faecal samples	89,6%	Croatia	Brnic´ et al, 2014
Faecal samples	38%	Ireland	O'Shea et al, 2016
Brain stem and spinal cord	60%	Hungary	Boros et al, 2017
Brain stem and spinal cord	100%	US	Matias et al, 2019
Faecal samples	83%	US	Rawal, Matias, Macedo, et al, 2019
Faecal samples	95.4%	Greece	Stamelou et al, 2022

Swine rotavirus is endemic in pig populations, and all swine herds certainly have a history of RV infection and circulation. Rotaviruses belong to the order *Reovirales*, family *Sedoreoviridae* which contains the genus *Rotavirus* divided into 10 species designated Rotavirus A to J. Rotaviruses are non-enveloped, icosahedral viruses 75 nm in diameter and composed of a triple layer capsid. The genome consists in 11 linear dsRNA segments and is formed in a unique morphogenic pathway, which involves acquisition of a transient lipid envelope during budding of immature particles into the endoplasmic reticulum (ER) (www.ictv.global).

Each of the rotavirus species infects a wide variety of animal species. Humans are infected with rotaviruses belonging to Rotavirus A, B, and C species, while pigs are infected with Rotavirus A, B, C, E, and H species (Norman et al, 2014; Kwot et al, 2020; Vlasova et al, 2017). In addition to humans, Rotavirus A, the most common Rotavirus species, can be found in pigs, monkeys, cattle, sheep, horses, dogs, cats, mice, rabbits and birds. Rotavirus B species also infects cattle, sheep, and rats, while Rotavirus C species also infects dogs, cattle, and cats (Martela et al, 2010). Rotavirus E is poorly documented, not making part of the species ratified by the ICTV and Rotavirus H, although prevalent in a few studies (Molinari et al, 2015), is only very rarely found and reported (Marthaler et al, 2014).

Rotavirus A (RVA) and C (RVC) are the most common among all RV species reported in swine. RVA was considered most prevalent and pathogenic in swine; however, RVC has been emerging as a significant cause of enteritis in newborn piglets. Since no intra-uterine passage of immunoglobulins occur in swine during gestation, newborn piglets are highly susceptible to RV infection at birth. Moreover, rotaviruses are constantly evolving, either by point mutation or as a result of genetic reassortment and many unusual human and/or animal strains have emerged in many countries (Santos N & Hoshino Y, 2005) and the list of human rotavirus strains that can recognize being a genomic segment of animal origin is far from complete.

The structural proteins of the inner capsid VP7 and the outer capsid VP4 correspond to the G (Glycoprotein) and P (protease-sensitive) antigens respectively inducing the production of neutralizing antibodies. Thus, these antigens have made it possible to define the types G and P of the viral strains and thus to better understand on the one hand the predominant strains in human diarrhea and on the other hand to compare them with the strains isolated in animals with a view to identify a possible zoonotic risk. The comparison of the genetic sequences made it possible to show the existence of a close relationship between certain animal and human rotaviruses or to discover new human genotypes which could recognize an animal origin, demonstrating that the specificity of host could be broken easily. Since the new virus classification system defined by Matthunssens et al (2008), there is a better understanding of the complex interactions between human and animal rotaviruses. Currently there are at least 23 G (VP7) and 32 P (VP4) genotypes identified.

As early as 1996, it was shown experimentally that the Wa strain of human rotavirus G1P (Matthijnssens et al, 2008) was pathogenic in gnotobiotic pigs (Ward et al, 1996). In addition, only pathogenic human strains cause diarrhea in pigs while attenuated human strains do not (Azevedo et al, 2005), allowing the porcine model to be used in assays to verify the efficacy human rotavirus vaccines. In Europe, human strains of rotavirus resembling porcine strains of group P (VP4) have often been identified (Yuan et al, 2006) and other serotypes of porcine origin have been noted in infantile diarrhea observed in non-European countries (Brazil, Argentina, Paraguay, India, Thailand) (Martella et al, 2010). The presence of porcine rotavirus group C was also proved detected in a Brazilian child with diarrhea (Gabbay et al, 2008). It was highlighted the striking contrast between the low genetic diversity of the human strains isolated in group C (responsible for cases of diarrhea with hospitalization in less than 5% of children) and the great variability of the porcine strains of this group.

Swine Calicivirus belongs to a large viral family, *Caliciviridae*, of the order *Picornavirales* infecting a wide variety of animals. This family includes a total of 11 different genera, including the *Norovirus* and *Sapovirus* genera, both of which infect humans and pigs and cause gastroenteritis. The genera *Norovirus* and *Sapovirus*, have only one species, respectively Norwalk virus and Sapporo virus (www.ictv.global). Another recently discovered genus, *Valovirus*, including Saint Valerian virus can also be found in the gastrointestinal tract of pigs (Desselberg, 2019).

Calicivirus virions are 27–40nm in diameter, non-enveloped with a single-stranded, positive-sense genomic RNA of 6.4–8.5kb organized into either two or three major ORFs. Generally, caliciviruses are stable in the environment and enteric caliciviruses are acid-stable. Genotyping based on the complete capsid region (ORF2 and ORF3) was until recently the gold standard (Vinje et al, 2004) for noroviruses, but RNA recombinations make the task more difficult (Bull et al, 2008). The latest classification has 10 genogroups and p-groups (GI to GX), 49 genotypes (9 GI, 27 GII, 3 GIII, 2 GIV, 2 GV, 2 GVI and 1 each of GVII, GVIII, GIX and GX) and 60 p-types (14 GI, 37 GII, 2 GIII, 1 GIV, 2 GV, 2 GVI, 1 GVII and 1 GX).

A universal nomenclature has been proposed to use when depositing new norovirus sequences: Organism/Host/2-letter country code/Year of sample collection/Genotype[p-type]/Sample name.

Genogroups GI, GII and GIV infect humans, and only genotypes GII.11, GII.18 and GII.19 have been detected in pigs (Chhabra et al, 2019).

The detection of *swine norovirus* dates back to 1997 when Sugieda et al. reported for the first time the presence of norovirus particles in swine faeces collected in Japan. Noroviruses of animal origin could infect humans, these are genogroup II noroviruses. Some have been detected in asymptomatic pigs in the Netherlands (Van der Poel et, 2000) and Japan (Sigieda et al, 1998). The detection of this virus in the faeces of sick domestic animals shows that it could be a zoonosis without knowing exactly how these viruses circulate from animals to humans and vice versa or whether the animals represent a reservoir of these pathogens for humans (Table 2).

Table 2.

Epidemiology of swine norovirus in European countries

Genotype	Overall detection	Country	Authors
GII.11 and GII.18	1,2%	Slovenia	Mijovski et al, 2010
-	12.2%	Spain	Halaihel et al, 2010
GII	5.8%	Hungary	Reuter et al, 2007
GII.19	4.6%	Belgium	Mauroy et al, 2008
GII.11	0.5%	Italy	Di Bartolo et al, 2014
GII.18	14.2%	Germany	Machnowska et al, 2014
GII.P11	2.53%	Italy	Laconi et al., 2020,
GII.P11 and GII.P18	11.4%	Italy	Cavicchio et al., 2020

In 2020, human noroviruses and other caliciviruses were the fourth most frequently reported causative agents of food and waterborne outbreaks in the European Union, associated with 130 outbreaks in thirteen member states (i.e., Belgium, Czechia, Denmark, Finland, France, Germany, Italy, Latvia, Malta, the Netherlands, Poland, Spain, and Sweden).

Sapoviruses is classified in 19 genogroups, subdivided into a total of 52 genotypes, based on the nucleotide sequence of VP1. Human sapoviruses are divided into 7 genotypes from each of the first 2 genogroups (GI.1 to GI.7 and GII.1 to GII.7), GIV and 2 genotypes of GV (GV.1 and GV.2) (Oka et al, 2015). Sapoviruses from pigs and wild boars are divided in 8 genogroups and 21 genotypes: GIII, GV.3 and 5, GVI.1 to 3, GVII.1 to 6, GVIII.1 and 2, GIX.1 to 3, GX 1 and 2 and GXI 1 to 3 (Sunaga et al, 2019).

The first particles of sapovirus were found in human faeces by electron microscopy during manifestations of clinical signs of diarrhea in 1976 in the United Kingdom, then recognized as pathogens causing gastroenteritis. Epidemics of sapovirus gastroenteritis are fewer than those of norovirus in humans.

Sapovirus RNA has frequently been detected in pig faeces, being found worldwide. The prevalence of porcine sapovirus vary greatly between countries, 30.4% in Brazil (Barry et al, 2008), in 75% of farms in Canada (L'Homme et al, 2009), 28.6% of farms in China (250), and also in

different farms from Denmark, Finland, Hungary, Italy, Slovenia and Spain (Reuter et al., 2010). The age group with the highest prevalence of sapovirus in pigs is 2 to 8 weeks.

Although there have been no cases of human infection from either porcine norovirus or sapovirus, there are still several factors that cause these viruses to be categorized as viral agents. potentially zoonotic. These two viruses have diverse genetic material, divided into multiple genogroups, but still have genogroups common to pigs and humans such as norovirus GII and sapovirus GV. Recombination events can occur in RdRp and VP1 regions within these genogroups (Wand et al, 2005). In addition, replication of a human GII norovirus has been demonstrated in gnotobiotic piglets (Cheetham et al, 2006) and antibodies against human noroviruses have been found in pigs in Venezuela (Farkas et al, 2005). The emergence of new strains with genetic material recombinant would be most likely to occur in countries where high livestock densities are close to human populations and where farming practices create close contact between humans and pigs.

Hepatitis E virus is classified into the *Hepeviridae* family. The family *Hepeviridae* includes enterically transmitted quasi-enveloped (blood or tissue culture) or non-enveloped (faeces) positive-sense single-stranded RNA viruses infecting mammals and birds (subfamily *Orthohepevirinae*) or fish (*Parahepevirinae*). Members of the subfamily *Orthohepevirinae* infect humans (genera *Paslahepevirus*) and domestic and wild mammals (genera *Rocahepevirus*) (Purdy et al, 2022). Although hepatitis E virus (HEV) is shed through faeces as a non-enveloped virus there is evidence that, HEV can hijack host membranes on assembly and exit. Possession of a host-derived envelope may allow the virus to circulate in a patient's blood escaping detection by neutralizing antibodies (Yin et al, 2016).

Hepatitis E virus infections are found worldwide in human and swine population. Different genotypes infect humans and can be divided into two different groups: genotypes 1 and 2, found in endemic areas, in developing countries where sanitary conditions are poor and genotypes 3 and 4 in sporadic cases, in industrialized countries. Genotype 7 has only very rarely been found in humans.

Over the past 2 decades, evidence has accumulated implicating pigs and other animals in the zoonotic transmission of G3 HEV to humans. In swine, hepatitis E virus infections are attributed to genotypes 3, 4 and 5, in the same regions where the virus is sporadic in humans. Genotype 3 infections in pigs have also been found in areas where the hepatitis E virus is endemic in humans (Pischke et al, 2013).

Table 3.

Hepatitis E virus molecular detection in pig food products in Europe

Country	Food product	ARN prevalence	Authors
UK	pig liver	3%	Berto et al, 2012
	sausages	10%	
France	pig liver sausages	30%	Pavio et al, 2014
	dry salted liver	3%	
	liver quenelles	25%	
Germany	liver sausages	22%	Szabo et al, 2015
	raw salami	20%	
Netherlands	cervelat	10.8%	Boxman et al, 2020
	salami	18.5%	
	metworst	26.1%	
	snijworst	16.3%	
Switzerland	raw liver sausages	11.8%	Giannini et al, 2017
Switzerland	meat products	11.1%	Moor et al, 2018
	liver sausages	18,9%	
	raw meat sausages	5.7%	
France	porc liver	2.8%	Feurer et al, 2018
Italy	traditional pork meat products	0%	Montone et al, 2019
	wild boar homemade meat and liver sausages	6.3%	

Result of the studies developed in UK and Switzerland (Dalton et al, 2007; Fraga et al, 2017) identified that indigenous cases of HEV were occurring in economically developed countries (Table 3). It is now widely accepted that pigs are a zoonotic source of HEV transmission, though increased detection and awareness of HEV may also play a small role in the observed increase in cases. There is a risk of contracting HEV from undercooked pig products, and there is also potential for other livestock species to be unidentified hosts for the virus. Generally, foodstuffs containing raw pork meat is more likely to cause a foodborne infection than cooked foods due to no thermal inactivation of the virus.

Some strains included in genotypes 3, 4 and 7 of the hepatitis E virus have been identified as zoonotic strains of the hepatitis E virus. Several cases of transmission to humans of viral strains infecting pigs and vice versa have been listed, as well as the ingestion of camel meat contaminated with genotype 7 of the hepatitis E virus (Lee et al, 2016). The pig would therefore be the primary reservoir of the hepatitis E virus in sporadic, non-endemic areas due to the autochthonous nature of the infections.

Consumption of raw or undercooked meat, game meat (Kamar et al, 2012), figatelli (a fresh sausage made from pork liver, smoked or dried) (Pavio et al, 2014), liver pâtés (Diez-Valcare et al, 2012) are known sources of zoonotic hepatitis E virus infection.

In conclusion, efforts devoted to the implementation of biosecurity measures are necessary, because swine viral infections are contagious and may cause harmful clinical manifestations that can cause great economic losses either by growth retardation or by the death of the animals. Viral infections in swine can cause several different pathologies, including polysystemic diseases, respiratory, urinary and reproductive system, skin and intestinal system, whose dysfunctions causing diarrhea are common problems in pig farms. These diarrheas can be caused by different pathogens, including many viral infections with zoonotic character. The control of zoonotic viral diarrhea requires a holistic view, including several factors such as washes and disinfection, immunity, pathogen treatments, gut microbiota, nutrition, stress reduction, and effective management practices. Pigs can act as intermediate and amplifying hosts for the viruses with zoonotic potential, thus the One Health approach should be applied in order to prevent the complex represented by public and animal health issues.

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