O objetivo desta revisão foi alertar veterinários e técnicos brasileiros que atuam na cadeira produtiva suínica sobre a Diarreia Epidêmica dos Suínos, que é causada por um vírus altamente infeccioso da família Coronaviridae que acomete o intestino ocasionando surtos agudos de diarreia e vômitos, com altas taxas de mortalidade de leitões lactentes. Em 2013 nos Estados Unidos a doença infectou, nas granjas, muitos animais de todas as idades, chegando a 100% de mortalidades dos leitões lactentes. Pela capacidade do vírus de se disseminar, a diarreia epidêmica dos suínos é um problema econômico e sanitário que requer medidas de biossegurança eficiente, vigilância das fronteiras e controle de entrada de material genético e de insumos, afim de bloquear a entrada do vírus no Brasil.

**Palavras-chave:** suinocultura, PEDv, Coronavirus, enfermidade emergente

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The aim of the current review is to alert the Brazilian veterinarians and technicians who work in the pig production chain about the Porcine Epidemic Diarrhea, which is caused by a highly infectious virus from family Coronaviridae. Such virus affects the animal’s intestine and causes acute diarrhea and vomiting outbreaks. It shows high mortality rates among suckling piglets. The disease has infected many animals of all ages in the US farms and reached 100% mortality among suckling piglets in 2013. The porcine epidemic diarrhea is an economic and health issue that requires measures such as efficient biosecurity, border surveillance, and the control of genetic material and inputs entry in order to block the virus access to Brazil, given the virus capacity to spread.

**Keywords:** pig farming, PEDv, Coronavirus, emerging disease
INTRODUCTION

The Porcine Epidemic Diarrhea or PEDv, acronym of the English name Porcine Epidemic Diarrhea Virus, was the enteric disease of greatest economic significance in pig farming in 2012 and 2013 (STEVenson et al., 2013). It is a viral contagious and infectious disease, which affects pigs of all ages and causes watery diarrhea, vomiting, rapid dehydration, and high morbidity and mortality (SONG and PARK, 2012).

The high mortality rate among piglets has decreased the number of animals available for slaughter in the United States, Canada and Mexico, and it has caused great economic loss not only for breeders, but for the entire pig meat chain as well (GOEDE and MORRISON, 2014).

According to United States Department of Agriculture (USDA) data (2016), Brazil is the fourth largest pork meat producer and exporter of pork and, in 2015, achieved an increase of 5.7% in pork meat production and exported 550,000 tons per year. This is due to the investments made in new technologies, equipment, breeding, nutrition and health of breeding stock. Thus, the Brazilian pig production can meet the desires of consumers for a healthy, safe and cheap food.

In order to Brazilian pig production continues to grow and to gain the international meat trade, it is necessary to keep the flocks with a high level of health. Therefore, diseases such as PED leads to health and economic issues and requires strict biosecurity measures, as well as permanent border surveillance and the control of genetic material and inputs entry in order to block the virus access to Brazil.

History

The PEDv was described in England in 1971, as well as in Belgium. At that time, it was named Epidemic Viral Diarrhea (EVD) and affected both growing and finishing animals. However, when the disease started affecting suckling piglets and adult animals in 1976, it came to be called, respectively Type I and Type II EVD (WOOD, 1977; PENSAERT and DEBOUCK, 1978).

The virus has spread to other European countries, such as Spain and Italy, and emerged in Asia (Japan, South Korea and Thailand) in the 1980s (PENSAERT and YEO, 2006). It was diagnosed in the United States in May 2013 (STEVenson et al., 2013). Given the increasing number of cases, the virus has reached 25 American states in 2015, as well as other countries in the continent such as Canada, Mexico, Peru and Colombia. There was no evidence of PEDv occurrence in Brazil until November 2015; however, it is not subject to compulsory notification to the OIE - World Organization for Animal Health (ZANCHIN et al., 2013). Therefore, the Brazilian authorities should adopt measures to prevent the disease from entering the country, since the land borders between Brazil and countries such as Peru and Colombia increase the risk and facilitate the introduction of PEDv in the national territory (STEVenson et al., 2013).

Etiology

The Porcine Epidemic Diarrhea virus belongs to family Coronaviridae, subfamily Coronavirinae, genus Alphacoronavirus. It has single-stranded, enveloped RNA, as well as positive-sense strand RNA of approximately 28 kb, and belongs to the group 1a of the genus (CHEN et al., 2010). The microbiological features of such virus are similar to those of the transmissible gastroenteritis (TGE) virus; they are just distinguishable through laboratory tests (NFT ALLIANCE, 2014).

There is 99.5% genetic similarity between the Asian coronavirus, which was isolated in 2012, and the US one, probably due to the introduction of the Asian virus in the American continent. Since then, genetic recombinations may have occurred and led to different forms of the virus (HUANG et al., 2013).

However, there is great controversy about this issue; according to Huang et al (2013), the last batch of animals introduced in the United States came from China. The animals tested negative for PEDv virus and showed no symptoms at all. Therefore, it is speculated that the virus must have entered the country through different routes, probably through animals coming from Canada or through pig feed imported from China (HUANG et al., 2013).

The virus is able to adapt itself and it resists well at pH 5 to 9, fact that hinders its inactivation through pH variation. It can survive for up to 2 weeks at room temperature. On the other hand, it is possible inactivating it at the temperature of 60°C for 30 minutes (SONG and PARK, 2012). The virus is sensitive to formalin (1%), anhydrous sodium carbonate (4%), and to lipid solvents such as chloroform, iodophors in phosphoric acid (1%) and sodium hydroxide (2%). It is able to survive for 28 days in the mud at 4°C, for 7 days in the feed dried at 25°C, and it is inactivated at temperatures higher than 60°C (OIE, 2014).

Epidemiology

The large amount of virus excreted in the feces (DUFRESNE and ROBBINS, 2014) and its 2-week survival in the facilities – since it is necessary heating it at 60°C for 30 minutes in order to inactivate
it (PENSAERT and YEO, 2006) - may explain the rapid spread of the disease.

The number of cases in the US increases during autumn because the virus survives for longer under wet and cold conditions (PEET, 2014).

The PEDv easily spreads through the transportation of pigs; through humans, in their clothes and boots; and through any equipment or inanimate object brought to the production unit. The feed and its ingredients may carry the virus and be mechanically spread by birds, insects and other animals. Air spread has been demonstrated, but only over short distances, and it is unlikely to be the determining factor in the spread of the virus (WADDOLOVE, 2014).

The infection may become subclinical or intermittent and show fluctuations at the immunity level of the herd after the outbreak phase. It may manifest through occasional diarrhea in suckling piglets. The main mode of transmission is the fecal-oral route or through contaminated fomites; however, there is no major vector or reservoir (SAIF et al., 2012).

According to Saif et al. (2012), the most concerning PEDv aspect is the high mortality rate found in pigs of all ages, especially among piglets in the farrowing phase, when the most severe form of the disease occurs.

The animals may present varying morbidity and mortality rates during outbreaks depending on the susceptibility of the herd, i.e., on the previously established immunity degree, as well as on the virulence degree of the PEDv isolate in question (ZANCHIN et al., 2013).

Infected pigs have been found in US farms during the finishing phase, since there are multiple shipments to slaughterhouses not subjected to previous decontamination (LINHARES, 2014).

The lesions in the intestinal villi lead to malabsorption of nutrients, which is caused by cell degeneration, villous atrophy, vacuoles in the enterocytes, adherence and damage in the tight junctions between the enterocytes and in the connection between the junctions and the lamina propria. The top of the villi suffers erosions or the cells change from cuboid to squamous (PENSAERT and YEO, 2006; MADSON et al., 2014).

There is the belief that the epithelium of the intestinal mucosa is the PEDv target. However, Park and Shin (2014) reported PEDv replication not only in the small intestine, but also in the pulmonary alveoli macrophages. The PEDv infection and replication in the respiratory tract of naturally infected pigs was identified through RT-PCR, immunohistochemistry and virus re-isolation. The discovery that PEDv infects and replicates in alveolar macrophages provides new horizons about its pathogenesis.

Phisiopathogenesis

The PEDv and the transmissible gastroenteritis (TGE) virus in pigs are genetically and antigenically different; furthermore, PEDv appears to be much more pathogenic than the TGE virus.

The PEDv has short incubation period of approximately 1-2 days and it continues to be secreted for 7 to 11 days (SAIF et al., 2012).

After the fecal-oral transmission, the virus infects the enterocytes and leads the affected pigs to villus atrophy, watery diarrhea, vomiting and anorexia (DEBOUCK and PENSAERT, 1980). The symptoms appear fast, between 22 and 36 hours after the oral inoculation of the virus, in 3-day-old pigs (DEBOUCK et al., 1981). According to Goede et al. (2015), the disease causes 100% mortality among the affected nursing piglets, 4 to 5 weeks after infection. After such phase, the herd develops immune response and the matrices start transferring immunity to the piglets through the colostrum, which helps reducing piglet mortality to acceptable production rates. Older animals show appetite loss, delayed development, vomiting and diarrhea. Since the virus is species-specific (SAIF et al., 2012), the disease is not classified as zoonosis, therefore, it poses no risk to other animal species or to humans (NFT ALLIANCE, 2014).

The disease is more severe in young pigs; however, it may affect animals of all ages, thus leading to death or production loss (SUINOCULTURA INDUSTRIAL, 2014).

The decrease in enzyme production and in the absorptive capacity of the small intestine results in malabsorption- and maldigestion-related diarrhea, although they are not pathognomonic lesions of PEDv (JUNG et al., 2006).

It takes approximately 4 to 5 weeks for the infected females to develop immunity; however, there is high mortality rate during this period, which may reach 100%. After this period, the females develop immune response and transfer the antibodies to their offspring through the colostrum. Such fact decreases the mortality rate among piglets (GOEDE et al., 2015).

It is worth highlighting that the PED virus affects pigs only. It has no zoonotic nature and the pig meat consumption causes no harm. According to the World Organization for Animal Health,
nowadays, the PED is not subject to compulsory notification (WEIBLEN et al., 2012).

Clinical signs

Piglets affected by PEDv may not show obvious symptoms, and it makes it difficult to detect the disease (PEET, 2014).

The clinical signs of PEDv are very similar to those of TGEv; both viruses lead to the atrophy and destruction of the villi in both the jejunum and the ileum. Despite these similarities, the viruses are different. The progression of the intestinal infection caused by PEDv is slower than that caused by TGEv. In addition, the viral nucleic acid of the PEDv is detected 24 hours after inoculation and that of the TGEv, 12 hours after it (KIM and CHAE, 2002). Thus, the longest incubation period observed in PEDv due to the low infection rate, as well as to the fact that the PEDv replication is restricted to the epithelial cells that cover the villi in the gastrointestinal tract (KIM et al., 1999; KIM and CHAE, 2000).

The clinical signs of TGE and PED are similar in young animals; therefore, the diseases must be differentiated through laboratory diagnosis, mainly through PCR (PENSAERT and YEO, 2006).

The differential PED diagnosis should take neonatal colibacillosis, clostridiosis, Isospora suis, TGE and infections caused by type A rotavirus into consideration, mainly in herds showing no immunity degree against these agents.

Diagnosis

The clinical diagnosis may be based on the history of diarrhea, severe dehydration and vomiting, which must be confirmed through polymerase chain reaction (PCR) (ZANCHIM et al., 2013), multiplex real time polymerase chain reaction (RT-PCR) (KIM et al., 2007), multiplex reverse transcription-nested polymerase chain reaction (RT-nPCR) (JUNG et al., 2003) or reverse transcription loop-mediated isothermal amplification (RT-LAMP) (REN and LI, 2011) in order to detecting PEDV from clinical samples and differentiating PEDV from others porcine diseases which are clinically similar to PEDv, such as porcine transmissible gastroenteritis virus (TGEv) and porcine rotavirus (JUNG et al., 2003; KIM et al., 2007; REN and LI, 2011). Diagnosis can also be reached through rapid serological tests such as Enzyme Linked Immunosorbent Assay (ELISA) (ZANCHIN et al., 2013). Besides, other diagnosis methods can be use such as electron microscopy, immunohistochemistry, serology, immunochromatography (SUN et al., 2014) and in situ hybridization (KIM and CHAE, 2000).

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Treatment

No curative treatment has been developed so far, just symptomatic ones such as providing water to minimize dehydration and using hydrating solutions such as support therapy, administration of egg yolk with anti-PEDV immunoglobulins (SHIBATA et al., 2001).

Prevention and control

Care should be taken so that the virus does not get to PED-free farms in order to prevent the disease from spreading further. According to the American Association of Swine Veterinarians (AASV), biosecurity measures should be adopted, namely: putting replacement animals into quarantine; changing clothes and shoes before going in and out the farm; providing farm clothes to veterinarians and staff; limiting the access of people who are not involved in the work developed at the farm; adopting rigorous procedures to disinfect the vehicles that transport animals and feed; prohibiting the access to any visitors, suspending the imports of raw materials of animal origin, or whenever necessary, performing molecular tests such as PCR in order to investigate the presence or absence of the virus; and taking all the basic farm management procedures very seriously - managing the colostrum, implementing an everyone in/everyone out system, thoughtfully cleaning and disinfecting the facilities, controlling vectors, rodents, flies and birds, and using disinfectants with proven virucidal action (WEIBLEN et al., 2012).

The prevention procedures adopted in PEDV-positive farms comprise weaning the piglets in order to avoid high mortality rate, since newborns have not yet developed the necessary immunity to face such virus. In addition, the gilts are exposed to the virus in order to stimulate the production of antibodies and to passively transfer them to the newborns during lactation (PANZARDI, 2014).

The good immunity of gilts, which is developed after natural infection, may reduce the clinical impacts. A vaccine was produced after the new outbreaks between 2012 and 2015 have occurred, despite the difficulty of isolating the PEDV etiologic agent, in order to perform pathogenesis studies, to develop assays and diagnostic tests, as well as efficient vaccines (SUN et al., 2014).

Licensed vaccines are available in Canada and they seem to reduce the clinical severity of the disease, as well as the dissemination
of the virus in the infected farms. However, biosafety is the most efficient way to stop propagation; eliminating the virus is the key to prevent the disease and to achieve the clinical recovery of the affected animals (WADDILOVE, 2014).

Biosecurity programs require planning, incorporating good practices and training people, as well as the appropriate use of disinfectants in the facilities, equipment and, mainly, in the vehicles that transport animals and feed (WADDILOVE, 2014). According to Linhares (2014), 11.4% of the vehicles were contaminated after the animals were delivered to American slaughterhouses. These data demonstrate the PEDv spread and highlight the importance of implementing biosecurity transportation programs in order to have more effective and efficient control of the disease in prevalent countries. Properly choosing the disinfectant is vital; it needs to be active against PEDv and must also have broad spectrum of activity against other pathogens affecting pigs. Detergents are an essential part of good cleaning since they are able to reduce contamination by 60% during washing. The simultaneous use of detergents and disinfectants reduces contamination by 99% (WADDILOVE, 2014).

The use of separation lines between the clean and dirty areas, for example, between the loading ramp and the pig carrier, or between the ground and the cabin of the feed delivery vehicle is a major improvement in the biosafety program. The control of birds, rodents, insects and other animals should be reviewed. In addition, the sharing of equipment, personnel and transport material with positive or negative units should be avoided. Staff training and recycling is an integral part of any biosecurity program and it should comprise managers, farm teams, drivers, service personnel and visitors, so they can understand why biosecurity against PEDv is important and how the virus easily spreads (WADDILOVE, 2014).

Biosecurity is the key to prevention. In addition, there is close cooperation among all members of the pig production chain, including truck drivers, processing units and veterinarians (PEET, 2014).

Some American farms have adopted closure procedures for at least six months. The gilts are introduced as long as there is no evidence of virus circulation in the herd or after the susceptible gilts are subjected to quarantine and tested negative for 60 days. The implementation of disease combat programs requires investigating the origin / source of the infection in the farm in order to control it and to reduce the risk of reinfection (ZANCHIN et al., 2013).

The biosecurity program against PEDv should encompass the performance of laboratory analysis in order to detect the disease at the site, as well as the monitoring of critical areas for possible transmission such as processing units, unloading docks, trucks and truck-washing facilities (PEET, 2014).

**Perspectives**

Some countries have already banned the imports of animals from positive countries, as well as of pork by-products used to feed animals. China and Japan have already restricted the imports of US pork. However, France was the first European country to take such measure (NFT ALLIANCE, 2014).

The productive sector has been increasingly concerned about the arrival of the PED virus in countries such as the Dominican Republic, Colombia and Peru. In April 2014, the Brazilian pork industry has asked the Ministry of Agriculture to temporarily suspend the imports of live pigs (breeding animals), as well as of porcine genetic material and plasma from the US, as a preventive measure to the emergence of PEDv cases in Brazil, although measures had already been implemented to assure the health of imported breeding animals. There are suspicions that the plasma used in pig feed, as well as other inputs, may be the most probable source of contamination (SUINOCULTURA INDUSTRIAL, 2014).

In face of a possible suspicion or even of the confirmation of a PEDv case in Brazil, the main actions to be immediately taken would be: interdicting the suspected farm; applying control and containment protocols; identifying the routes and modes of transmission; controlling the traffic of vehicles and people in positive farms; registering the animals; keeping absolute control over the destination of the dead animals and farrowing remains; and requiring people who enter the farm to take a bath and change their clothes before they come in (BRASIL, 2015).

The health authorities should be immediately notified if any positive case is found in Brazil, so that the necessary measures can be taken in order to prevent the virus from spreading throughout the country, as well as to prevent the disease from taking greater proportions (WEIBLEN et al., 2012).

The health authorities should be immediately notified if any positive case is found in Brazil, so that the necessary measures can be taken in order to prevent the virus from spreading throughout the country, as well as to prevent the disease from taking greater proportions (WEIBLEN et al., 2012).
The Brazilian Ministry of Agriculture, Livestock and Supply (MAPA - Ministério da Agricultura, Pecuária e Abastecimento) has increased the rigor of sanitary requirements toward the imports of high-genetics live pigs, genetic pig material and inputs for feed after the PEDv outbreaks in the US, in May 2013. The Animal Health Department (DSA – Departamento de Saúde Animal) of MAPA ruled that all import requests must be submitted for analysis and approval by the Department, exclusively, in Brasilia (BRASIL, 2014a).

The animals must come from certified institutions and the absence of the disease in the last twelve months must be inspected by the official veterinary officer from the country of origin. The animals must be subjected to quarantine in the country of origin before they are transported to the Brazilian farms (BRASIL, 2015). All pig imports to Brazil will occur just after the tests in the country of origin are conducted and after the animals are subjected to quarantine of at least 30 days in Cananéia Quarantine Station. The Station is the only establishment regulated by MAPA to receive imported animals and to issue certificates approving the animals after their health status is proven. Thus, it rules out the possibility of diseases such as PED, among others, to enter the country are not yet known, since there is no positive diagnosis for PEDv in Brazil and since some measures concerning the imports of products and genetic material are still being analyzed by the competent bodies to avoid the possible introduction of the agent in Brazilian herds (NFT ALLIANCE, 2014).

Similar to Canada, it is worth making the producers, as well as all people working in productive chain points, aware of PEDv severity and organizing teleconferences and meetings between producers and technicians in order to exchange information, experience and to conduct trainings. (PEET, 2014). National conferences with technicians and breeders should be held in order to upgrade and disseminate the knowledge about the disease and about the importance of adopting strict biosecurity measures in the farms, especially with regard to the input and output of farm products, as well as to the transit of people.

The epidemiological aspects of Porcine Epidemic Diarrhea must be further studied in order to enable the production of an effective vaccine able to enhance the global herd’s immunity and to reduce losses. The disease is exotic in Brazil; however, the country is vulnerable since it shares borders with countries where the disease has already been reported. Using the best prevention management practices and implementing biosecurity programs is essential for the country to remain free of such disease. Taking measures to keep the Brazilian pig herds free from the disease is a way to assure the health of the Brazilian pigs. It may provide the opportunity for the Brazilian products to reach markets such as Japan, South Korea, Mexico, Latin America, China and Russia, among others, which were once supplied by major exporting countries that were contaminated by PEDv.

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