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Porcine epidemic diarrhea: A retrospect from Europe and matters of debate

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ABSTRACT

A retrospect is given on the emergence of porcine epidemic diarrhea (PED) during the early seventies in Europe. While, at first, it appeared as a disease affecting feeder pigs, fattening- and adult swine, it later also became pathogenic for neonatal and suckling pigs hereby drastically increasing its economic impact. Isolation of the causative virus revealed a new porcine coronavirus, the origin of which has never been clarified. Pathogenesis studies with the prototype strain CV777 showed severe villous atrophy in neonatal pigs and the virus-animal interactions showed many similarities with transmissible gastro-enteritis virus (TGEV), another porcine coronavirus. Disease patterns in field outbreaks showed muchvariation but, while farm related factors played a role, possible genetic variations of virus strains in Europe have not been examined and are thus unknown. CV777 in experimental pigs caused diarrheal disease and mortality rates similar to those later encountered in Asia and more recently with the "original" US strains even though genomic typing of the prototype European strain have shown that it belongs to the S-INDEL strains. In Europe, PED has become endemic during the eighties and nineties and subsequently regressed so that, after 2000, swine populations in many countries have largely become seronegative. Sporadic outbreaks have recently reappeared showing a large variety of clinical outcomes.

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1. How it all began

In 1972, a veterinary surgeon in England (Oldham 1972) wrote a letter to the editor of "Pig farming supplement" entitled "How it all began". He described the appearance of a new disease on some English swine farms, characterized by acute watery diarrhea in feeder pigs, fatteners and sows while suckling pigs were not affected. The syndrome was called TOO, standing for "The Other One" or also "TGE2" and both these denominations referred to its clinical similarity to TGE, a common cause of viral diarrhea in pigs in Europe at that time. An important difference with TGE was, however, that neonatal pigs were not affected. Since these denominations were considered unsatisfactory from a scientific point of view, the name of the new syndrome was quickly changed to "Epidemic Diarrhea-ED".

The first ED outbreak occurred on a farm in the spring of 1971 and the second 6 months later, at a distance of 2 miles from the

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former. Suckling piglets were not affected but pigs of 10 weeks and older and also adults showed an acute diarrhea lasting one week. The outbreak lasted 3–4 weeks on the farm. During the autumn of 1971 and also the following winter, several new outbreaks were reported. A clinical diagnosis and possibility for differentiation from TGE was thus based on the high morbidity in fatteners and adult animals in the absence of disease in neonatal and freshly weaned pigs. In most of these diarrheal cases, TGEV was excluded by laboratory examination. The fact that ED was observed on farms with a recent history of a TGE outbreak, and thus in TGEV immune animals, increased the conviction that TGEV was not involved. During 1972, ED spread rapidly between pig farms, particulary fattening herds. Mortality was rare and the effect of an outbreak was estimated at about 2 weeks feed cost.

A similar disease pattern was observed during the early seventies in Belgium and a rapid spread occurred to neighbouring countries in Western Europe. Here also, suckling pigs were not affected and remained free of diarrhea even when their mothers suffered from a watery diarrhea during several days. Some neonatal pig mortality could occur by starvation because the sick mothers often suffered from agalactia.

An additional sign observed in Belgium and later also reported in Gemany, but not mentioned in England, was that some fatteners were found dead, particularly towards the end of the fattening period, and this occurred repeatedly in some farms but not in others. A mortality rate as high as 3% could be encountered. This was not due to dehydration accompanying the diarrhea but animals suddenly died from acute back muscle necrosis. While the clinical link with an ED infection was clear, the pathogenetic background has never been revealed. Belgian pigs were highly stress positive at that time and a severe belly ache often observed in adult animals during an outbreak of ED may have been a trigger.

In general, as no baby pig mortality occurred due to the ED agent, not very much attention was given to this new diarrheal syndrome and the etiology was not intensively investigated. However, it was assumed that a viral agent was involved since bacteriological examination of faecal material did not reveal a specific bacterial cause. None of the known porcine viruses could be associated and a new virus was, therefore, suspected.

2. Epidemic diarrhea (ED)1 towards epidemic diarrhea (ED)2

Much changed in 1976 when Wood (1977) from the Veterinary Investigation Centre in Norwich (England) described a new diarrheic syndrome. It differed from ED in that it now affected pigs of all ages, including neonatal and suckling pigs. Mortality was variable, restricted to young piglets and averaged around 30%. This new disease now resembled TGE more closely than ED did, but TGEV was again excluded using direct immunofluorescence on intestines and applying established serological techniques available for detection of anti-TGEV antibodies. Now, a differentiation with TGE on a clinical basis only became difficult, often impossible. This new syndrome was called ED2 to differentiate it from the 1971 ED1 where no baby pigs were involved. ED2 was economically much more important than ED1.

ED2 also quickly spread to the European continent and was recognised in Belgium in 1977. Reports from other countries including The Netherlands, Germany, France, Bulgaria, Hungary and Switzerland, followed soon. In Belgium, mortality rates in neonates on breeding farms varied considerably. They could be as high as 80% (large variation from 30 to 80%) and the average was 50%. Variation in mortality in neonatal pigs was litter bound, not explained at that time, but also farm bound where it appeared to be associated with farm size (still many small family farms at that time), farm structure (one or several farrowing units), number of neonatal pig litters present at the start of the outbreak, number of pregnant sows due to farrow within one week of the appearance of disease signs and possibly other factors. Differences in virulence of virus isolates was not given any attention.

This new evolution to ED2 with the involvement of baby pigs and its larger economic impact yielded better opportunities for collecting material for etiological studies, for experimental reproduction of the disease and for the development of virological and serological techniques. In 1978, Chasey and Cartwright (1978) reported the detection of virus like particles, and Pensaert and Debouck (1978) described the isolation of a new coronavirus-like agent (CVLA) from diarrheic pigs, with both research groups succeeding in reproducing diarrhea in experimental pigs. Soon after the isolation of this new coronavirus, extensive pathogenesis studies were performed in colostrum deprived pigs with one of the Belgian isolates, designated coronavirus CV777, (isolated in month 7 of 1977) which became the prototype strain for PEDV in Europe (Debouck and Pensaert, 1980; Debouck et al., 1981). ED2 was soon named "porcine epidemic diarrhea" (PED) caused by PED virus (PEDV) a denomination which still stands at present.

3. The PEDV after its first detection

From the early studies with PEDV in neonates (Debouck and Pensaert, 1980; Debouck et al., 1981) it was soon clear that the pathogenesis resembled very much that of TGEV. Experience gathered from research with TGEV helped much in the approach to study this new enteric disease. Lack of success to cultivate the virus in cell cultures forced to produce clean virus stocks by oral inoculation of colostrum deprived pigs, performing surgery 18 h later and rinsing the in vivo produced virus from the lumen of the infected small intestines during 12 h while keeping the pig in the incubator (Debouck and Pensaert, 1980). Such "clean" pig adapted virus stocks served for experimental pig inoculation experiments and to produce an hyperimmune serum for the preparation of a conjugate for an immunofluorescence (IF) conjugate to detect the virus in tissues. Serological tests were developed to detect antibodies by ELISA (Callebaut et al., 1982) and to study possible relationship with other coronaviruses by immuno-electron microscopy (Pensaert et al., 1981). Genome analysis of the PED isolate(s) was not available at that time.

By immuno-electron microscopy and IF, PEDV was not related to any of the known porcine coronaviruses (TGEV, Haemagglutinating encephalo-myelitis virus) (Pensaert et al., 1981). Some discrete relationship with members of the genus alpha-coronavirus was later demonstrated using other and more sensitive tests. The origin of PEDV was thus unknown and no potential parent coronavirus could be indicated.

An ELISA test was soon used for routine serology (Callebaut et al., 1982). A crucial question was whether or not the ED1 agent and ED2/PEDV were related or whether ED2/PEDV was totally new. Infectious material containing the ED1 agent from earlier outbreaks was not available. A retrospective serological survey was carried out on sow sera that had been collected in slaughterhouses in Belgium starting in 1969 and thus prior to the emergence of ED1 in 1972 on the European continent. Antibodies to PEDV were not found in sera collected in 1969 but were present in 7% of the sows collected in 1971, in 42% of the sows in 1975 and in 32% of the sows in 1980. These results indicated that the coronavirus PED had been responsible for first ED1 outbreaks, for the ED2 outbreaks and thus it can be accepted that PEDV emerged in 1971 but later widened its host tropism from growing and adult swine towards neonatal pigs. This finding was interesting from an evolutionary point of view.

Thus, PEDV that presumably started as a cause of diarrhea in 1971 in feeders, fatteners and adult swine, had suddenly acquired tropism for neonatal pigs and now became a rather devastating disease. But even after the emergence of ED2/PEDV, some outbreaks on breeding-finishing farms still did not involve neonatal pigs. While it was assumed that both ED1 and PEDV were co-circulating in the swine population, it is also possible that some farms had experienced an earlier ED1 infection and that immune sows protected their offspring against PEDV by lactogenic immunity while groups of fattening pigs had become susceptible. It must, however, be mentioned that cross-protection between ED1 and PEDV has never been studied. Also, after a first epidemic phase of the new PEDV, the virus often persisted on breeding-finishing farms in weaned and feeder pigs (endemic PED). The sow population was immune, protecting its offspring, while feeder pigs became susceptible after loosing their maternal protection. The highly variable and mixed clinical picture was, at that time, ascribed to the possible co-circulation of the original ED1 agent and its presumed variant PEDV in the population. Genome analysis was not available and ED1 infectious material is also now no longer available to retrospectively examine this issue.

ED2/PEDV is likely a variant of ED1. That variants of PEDV relatively easy emerge is not unusual as animal coronaviruses are known to easily undergo genetic alterations.

Recombination and insertions and deletions have repeatedly been demonstrated in PEDV by genome analyses of isolates during more recent outbreaks in Asia and in the USA (Fan et al., 2012; Li et al., 2016; Jarvis et al., 2016; Vlasova et al., 2014; Oka et al., 2014).

Even now (2016) in recent cases of PED in Europe, varying types of clinical manifestations, either with or without affection of neonatal pigs, are observed (see later).

The question on the origin of PEDV (and thus of its presumed ancestor ED1 agent) in 1971 is unanswered. There are no indications for a possible evolution from another known so called "parental" coronavirus, even after comparative studies with the known coronaviruses using detailed genome analyses of different genes including the S gene. So far, only discrete antigenic relationship involving the N protein but without any cross protection was detected with some of the other animal members of the genus alphacoronavirus such as feline infectious peritonitis virus (FIPV), TGEV, porcine respiratory coronavirus (PRCV), canine coronavirus (CCoV) and mink coronavirus (MCV). By the use of monoclonal antibodies to the N proteins of the human alphacoronaviruses NL63 and 229E, no cross reactivity was detected with PEDV (Sastre et al., 2011). The only alphacoronavirus in which also the M proteins cross reacts with PEDV is MCV (Have et al., 1992).

The nucleotide sequence of the PEDV nucleocapsid gene and of typical coronavirus motifs show that PEDV, within the region of the genome sequenced, shows indeed greatest homology to the human 229E, TGEV, PRCV, FIPV, CCoV and feline enteric coronavirus (FECV) (Bridgen et al., 1993). It is interesting to mention that, similar to PEDV, several of the other alphacoronaviruses, including the human 229E, TGEV, PRCV, CCoV, FECV and FIPV use the cellular receptor aminopeptidase N (APN) for virus entry into cells in their host (Weiss and Navas-Martin., 2005) and this seems to be a common evolutionary characteristic. Still, the genetic and antigenic diversity between PEDV and the other alphacoronaviruses is very largeAlso, no cross-reactivity has been reported between PEDV and the coronaviruses belonging to the beta, gamma or delta genera.The genomic data presented above and the use of the same cellular receptor suggest a common origin of some of some of these alphacoronaviruses. A carrier-wild animal species as source of the virus, as often described with other coronaviruses, cannot be excluded.

4. PEDV pathogenesis, virulence and genome characteristics

Soon after its detection, experimental studies in neonatal pigs revealed that target cells of PEDV were limited to the epithelium covering the intestinal villi and the pathogenesis was thus highly similar to that of TGEV (Debouck and Pensaert, 1980; Debouck et al., 1981). CV777 virus infection in the villous enterocytes in neonatal pigs caused rapid cell desquamation throughout the small intestine within 24–36 h after inoculation which was somewhat slower than observed with TGEV. Still, the villous atrophy induced by PEDV was so abrupt and extensive that rapid and severe dehydration occurred leading to death in neonatal pigs. Due to this similarity in pathogenesis with TGEV, much of the scientific knowledge acquired on TGE diagnosis, −immunity, −prevention could be almost invariably applied to PED. An apparent difference with TGEV, probably of minor importance from a clinical point of view, was that epithelial cells on colonic villi were also infected but desquamation was not observed. Still now, it is a question if this colonic site of replication contributes to disease severity. PED diarrhea in fatteners and sows is often accompanied by an apparent belly ache, a clinical sign not seen with TGE, and the question arises if the colon infection may contribute to this clinical manifestation.

Results of pathogenesis studies obtained in caesarean derived, colostrum deprived neonatal pigs upon inoculation with the European prototype strain CV777 of the seventies, were practically identical to those observed more recently in Asia and in the USA epidemics with the so-called "original US PEDV strains" (Jung et al., 2014; Stevenson et al., 2013; Kim and Chae, 2003).

A point of debate in the PEDV evolution, particularly since its occurrence in Asia and its emergence the USA, is the arising of PEDV genetic variants influencing virulence. The history in Europe, here presented, allows to assume that ED2/PEDV was a variant of ED1 which had acquired tropism for intestinal enterocytes in neonatal pigs. This new tropism expanded and increased the virus virulence since a vulnerable age became affected and piglets mortality became an important economic aspect of the disease. Currently, two major PEDV variants are described in the USA upon routine genome analyses of USA isolates. The first, also called "original US PEDV ", appears to be "highly virulent" while the second, the so called S-INDEL strains, standing for INsertions and DELetions in the S gene of the virus, are associated with mild(er) clinical outbreaks. Similar genotypic variants have been detected in Asia, the S-INDELs already before 2010 and the highly virulent since 2010. When adopting this genomic identification, it appears that CV777 is classified as a S-INDEL isolate apparently belonging to a different cluster compared to the US INDELs (Carvajal et al., 2015). Considering the pathogenesis and virulence of the European prototype strain CV777 of the seventies as evaluated by the sites and degree of replication and the degree of villous atrophy, no real difference exists with the more recent highly virulent (original US PEDV) isolates from the USA. For example, the pig adapted C777 when experimentally inoculated in neonatal piglets, caused villous atrophy with villous length reduction from the normal value of 700–900 μm to as low as 200–300 μm throughout the small intestine and within 6–36 h after the start of the diarrhea (Debouck et al., 1981; Coussement et al., 1982).

Much depends on how virulence of PEDV is determined. If virulence of a PEDV isolate is considered merely from the point of view of virus-neonatal pig interaction with parameters such as duration of incubation period, rapidity and severity of enterocyte desquamation, degree and extent of atrophy of villi, production of virulent virus quantities and severity of diarrhea, then CV777 can be classified as highly virulent despite its identification with S-INDEL isolates.

That S-INDELs isolates do not systematically mean low virulence was recently shown in a US study (Chun-Ming et al., 2015) in which 4 litters of 3–4 days old suckling pigs were inoculated with the S-INDEL Iowa 106 strain in the presence of their PED negative mothers. The severity of clinical signs and the mortality of the pigs varied between the 4 liters (from 0% to 75%). Severe clinical signs were observed in 2 of the 4 litters. Two of the 4 sows developed diarrhea. It was observed that, despite similar background of sows and environment in this experiment, the severity of disease was rather variable. It appeared that the pigs' body weight at birth and the sows health conditions and lactation were influential factors. In the same experiment mentioned above (Chun-Ming et al., 2015), one litter was also inoculated with an original US PEDV strain of high virulence. It was concluded that virulence of the S-INDEL isolate was generally lower based on the longer incubation period, the shorter duration of diarrhea, more limited regions of virus infection, overall lower pig mortality (18% vs 55% for "original") and some other additional parameters.

The sites and extent of the deletions or insertions and the seqence differences in the S gene may play an important role. In a recent publication (Chen et al., 2016) the pathogenicity differences between 3 U.S.PEDV prototype strains and a S-INDEL-variant stain were compared in conventional neonatal pigs under experimental infections and enteric disease, as evidenced by clinical signs,fecal virus shedding, gross and histopathological intestinal lesions, were significantly lower for the S-INDEL strain.However,the molecular basis for the virulence differences were not elucidated.

Since the early beginning in Europe, it was clear that PED disease can show much variability even in different litters of pigs particularly when suckling their mother. Such differences and the high variation in pig mortality in different litters (from 30 to 80%) was an observation also made in the seventies in Europe when the first epidemic occurred and the reason was never unravelled.

Even more variability is experienced when virulence and severity of PED disease is related to the interaction virus-farm population and thus in field outbreaks. The result of a PED outbreak will be much more difficult to predict, to evaluate and to define since, next to possible virulence differences of the isolates and next to variation among litters in suckling pigs, many additional factors play a role in determining the clinical outcome of the infection. They include immune status of sows, dose of virus exposure on the farm, herd size and pig farming management and others, all of which may be interacting in a different way. Moreover, the procedures applied for intentional infection (feed back) of the sow population to speed up the induction of immunity to be passively transfered to the litter could be considered as a potential cause of worsening of the clinical status of the suckling pigs. In fact, that practice can also be a source of other pathogens for gilts/sows and/or for newborn piglets. It is thus possible that, particularly in a fully susceptible pig population and even with PEDV strains of similar virulence, the mortality rates and losses are much higher in some continents or regions or farms with extensive and highly industrialised pig farming. The overall health status of the population apparently also plays an important role.

While genomic changes surely will occur in PED virus isolates, it is advised to be careful when associating them with virulence changes. When a different clinical picture is observed on farms, it is often too hastily concluded that variants with varying virulence have arisen based on genome analysis only and without testing for virulence factors in experimental pigs.

While genome analysis is certainly useful and may be directional, repeated comparative animal inoculation experiments with so called new isolates, clinically denominated as candidate "virulence-variants", need to be carried out in a standardized way before solid conclusions about virulence are made. This is indicated by the large variations very often observed with one and the same isolate. The neonatal, non suckling pig, preferably colostrum deprived, is reliable and even essential for this purpose. Parameters as duration of incubation period, a timewise follow up of site and degree of villous affection in the small intestine are needed and must be repeated before calling a PEDV isolate a variant with impact on virulence. It should be stressed that pig adapted virus strains should be used as it is known that major genomic modifications can arise when PEDV is cell culture passaged, as well in porcine as in non-porcine cells, such as in Vero cells.

5. Epidemiology of PEDV in Europe

The epidemiology of PED in Europe has been and still is quite puzzling. PEDV outbreaks in the late seventies and early eighties occurred both on breeding and fattening swine farms. Acute outbreaks with neonatal pig mortality were encountered in the breeding-fattening farms which became infected for the first time. PEDV often became endemic. In farrowing-finishing farms, successive groups of pigs became infected upon weaning and after losing their lactogenic protection from their immune mothers, so that the virus could persist. Whether the virus persisted or not after the original outbreak was somewhat unpredictable, as it could also disappear from the farm. The farm size (number of sows) and its structure (number of units) played a role. Also PED persistence regularly occurred in fattening farms using the system of continuous introduction of feeder pigs originating from numerous and different breeders. A typical case of persistent diarrhea caused by PEDV lasting 10 months on a breeding-finishing farm was described in the Netherlands (Pijpers et al.,1993) and this was a feature regularly observed in Europe in the eighties. Recent experience in the USA (2013–2015), has shown that management practices adopted in the epidemic phase of the infection can turn PED to a endemic/enzootic and long lasting form (Jung and Saif, 2015).

PEDV infections were a regular cause associated with viral diarrheal picture in weaned and feeder pigs. In a serological study in Belgium in 1986, PEDV was associated with diarrhea in 13 out of 16 groups of feeder pigs after arrival in fattening farms (Callebaut et al., 1986)

But, the virus remained prevalent in the swine populations of Western Europe during the eighties. A serosurvey in Belgian sows using sera collected in slaughterhouses, and thus mostly originating from different farms, showed PEDV antibodies 32% in 1980 and 19% in 1984. Similar percentages of sows were positive in Germany (on 3 regional locations), France, Spain, the Netherlands and Bulgaria while no antibodies were found in Scandinavia, Northern Ireland, USA or Australia (Debouck et al., 1982). In 1982, antibodies were detected in sera received from Taiwan (the first evidence of the presence of PEDV in Asia).

As the eighties advanced, fewer outbreaks on breeding farms were seen even though the virus was still detected but the general economic impact of PED had become lower. In Belgium in 1992, 17 groups of feeder pigs from 15 commercial finishing herds, using the all in-all out production system, were examined for seroconversion to PEDV and TGEV. None of the groups seroconverted to TGEV while 7 seroconverted to PEDV with diarrhea observed in all 7 (Van Reeth and Pensaert, 1994). In an Hungarian study published in 1996, 5.5% of 92 faecal samples from weaned pigs with diarrhea tested positively for PEDV (Nagy et al., 1996).

During the nineties, an acute PED outbreak which was described in Spain involving a fattening unit of 5000 pigs with diarrhea starting in 7–9 weeks old pigs in one barn affecting pigs from 20 to 90 kg and subsequently spreading to the other barns (Carvajal et al., 1995). An isolated outbreak was described, in 1998 in England, in a large finishing herd where weaners were brought in over a 2 month period and positive sows were found in the breeding herds supply-

ing the weaners (Pritchard et al., 1999). But, no further epidemic of PED occurred despite a very low PEDV seroprevalence as only 1.9% of fatteners from 64 different finishing units were positive for antibodies to PEDV(May 1996–January 1997).

Interest from a disease and economic point of view became very low in Europe and no further research was performed on PED. Practically no serosurveys were carried out. A serological survey in sows from farrow to finish herds carried out in Belgium in 1996 revealed that gilts were positive for PEDV antibodies in only 2 of the 144 considered farms, and in 1997, 72 fattening farms were examined for PEV antibodies and none were positive (Pensaert, unpublished).

It appeared that PEDV, except for a focal case, was disappearing from the European swine population towards the turn of the century. For this reason, no attention or follow up was given anymore to this viral infection while its field of interest had fully moved to Asia.

However, a somewhat atypical PED outbreak occurred unexpectedly in the Po Valley in Northern Italy in 2006, (Martelli et al., 2008). It occurred between May 2005 and June 2006 in an area densely populated with pigs. The outbreak started with four cases occurring in fattening farms from May to July. No clinical cases were detected during August and September. In October, two new cases appeared: the first in a fattening unit and the second in the nursery of a three-site production unit. The disease spread during the winter of 2005–2006, affecting more than 60 farms including fattening units as well as farrow-to-finish or farrow-to-weaner farms. Some PEDV positive farms were still detected between mid-2006 and the end of 2007, but the disease progressively disappeared (Sozzi et al., 2014). From 2008–2014, only sporadic outbreaks were observed in grower and finisher herds (EFSA, 2014). This epidemic in Italy in 2006–2007 inclined us to forecast a new episode of PED epidemics in Europe but it did not occur.

Recently and due to an increased attention following the 2013 epidemic in the USA, single or limited PED outbreaks have sporadically been diagnosed in Europe. One case in Ukraine, (Dastjerdi et al., 2015) occurred in a 5000-sow farm (240 farrowings a week) and mortality in pigs less than 10 days old approached 100%. The virus was closely related to "original US" strains reported form North America (sequence identity of 99.8%).

Isolates from other cases reported from Belgium (Theuns et al., 2015), Holland (Van der Wolf et al., 2015), France (Grasland et al., 2015), Germany (Stadler et al., 2015; Hanke et al., 2015) and Portugal (Mesquita et al., 2015) and Italy (Alborali et al., 2014) were, on the basis of genetic sequence, closely related to each other. When sequenced, they were classified as S-INDEL strains, and the German isolate showed 99.4% identity to the OH851 strain isolated in the USA in January 2014 (Vlasova et al., 2014). The size and clinical disease in these outbreaks were very variable. The outbreak involved in Belgium: 1 fattening farm (no mortality), in France: 1 farrow to finish farm (mortality 12% in pigs at one week and 25% at weaning), in Germany: 4 farms (2 fattening with 1.5% and 2% mortality, 2 breeding with 70% and no mortality, respectively) and in Portugal where it started in one farm (with pig mortality, but not further defined) and where the virus spread to 43 other pig farms during a period of 3 months. From these data, it can be seen that, again, there was much and unexplained variation in PED clinical disease and outcome. Except for the possibility of the outbreak in Ukraine, it is very doubtful that the other European isolates have anything to do with those involved in the US epidemic. Similar focal cases must have occurred in Europe before the US outbreak but were, most likely, neither recognized nor diagnosed nor reported as PED. S-INDEL strains have been present in Europe as CV777 appears to be the earliest known representative (Carvajal et al., 2015).

It is remarkable that, in many European Countries, no large epidemic occurred despite several indications that the breeding population in their densely populated swine raising regions is negative for antibodies to PEDV and thus presumably fully susceptible.

It is difficult to understand why a virus such as PEDV has gradually regressed in the swine population in Europe in the absence of any special control measures. Vaccination has not been applied and no control programmes have been installed. The puzzling aspect is that, during the last decennia, PEDV was and still is focally present in Europe and did not cause an epidemic despite the high numbers of susceptible-seronegative farms and despite the very dense swine populations in some regions.

One would expect that a virus such as PEDV, which replicates to very high titers in swine and which can easily and rapidly spread from one swine farm to another, would be able to maintain itself in the swine population. As previously explained, once an outbreak has occurred on a breeding farm, PEDV virus could persist easily when successive litters of pigs, after losing their lactogenic protection at weaning, become a susceptible target for infection. In fact, persistence for a virus such as PEDV would be almost as a "natural" feature similar to the endemic character observed with other porcine enzootic enteric viruses such as swine rotaviruses, swine enteroviruses and others. TGEV cannot serve as an example here because, in Europe, it has largely been eliminated from the swine population due to the emergence, in the early eighties, of the closely related porcine respiratory coronavirus (PRCV). PRCV is a TGEV deletion mutant which has acquired respiratory tropism and shows an epidemiological advantage of rapid aerogenic spreading while causing a protective immunity to TGEV. Endemic PRCV has thus "replaced" TGEV in Europe.

It would be interesting to study the mechanisms behind the regression/waning of PEDV in Europe. Could it be that the virus has a non swine ancestor which has temporarily become adapted to swine but which is not really swine-borne? Such evolution would not be unique for animal coronaviruses. Could it be that the virus can maintain itself in the population only when present at a sufficient high dose allowing it to continue the infection chain but once reaching a low level quantity,e.g on a farm basis, is not longer able to do so? The waning of PEDV has apparently not occurred in parts of Asia within its 2–3 decennia of presence on that continent to the same degree as it did in Europe, and it will be intriguing to closely follow the epidemiological course and evolution of PEDV in the USA, once the epidemic phase has passed.

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