Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Preventive Veterinary Medicine 122 (2015) 235–241

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

The dilemma of rare events: Porcine epidemic diarrhea virus in North America

Peter R. Davies*

Department of Veterinary Population Medicine, College of Veterinary Medicine, University of Minnesota, Saint Paul, Minnesota, USA

ARTICLE INFO

Article history:
Received 15 March 2015
Received in revised form 27 July 2015
Accepted 8 August 2015

Keywords:
Porcine epidemic diarrhea
Emerging diseases
Virome
Feedborne transmission

ABSTRACT

Porcine epidemic diarrhea virus (PEDV) has been recognized as a swine pathogen for 40 years, but until 2013 had not been detected in the Western Hemisphere. From originally causing a relatively mild and sporadic disease, PEDV has been more recently associated with severe outbreaks of diarrheal disease in Asia, and subsequently North America. PEDV shares some important characteristics with two major pandemic viruses (porcine reproductive and respiratory virus; porcine circovirus type 2) of pigs that have high rates of mutation and high host specificity, and appear to have been present in the swine virome for decades prior to emerging to cause severe clinical disease. A unique feature of the PEDV in North America has been the implication of feed as a vehicle for transmission, with particular concerns related to ingredients of porcine origin. The importance of relatively rare events in contributing to both the emergence and transmission of PEDV is discussed in relation to approaches for managing the associated risks.

1. Introduction

The emergence of porcine epidemic diarrhea virus (PEDV) in the western Hemisphere in 2013/14 is among the most significant events of transboundary spread of animal disease of recent times. The unanticipated appearance of a highly infectious agent that can cause explosive outbreaks with high mortality creates a pressure cooker environment with urgent questions about what has happened (how, when, from where, why, who) and even more urgent questions about what needs to be done, both immediately to limit the damage, and in the longer term to prevent other events. Both formal and informal systems to manage animal health risks associated with trade and commercial operations have evolved at multiple levels—international, national, provincial, industry and the individual farm (Zepeda et al., 2005; Pitkin et al., 2009). All face the task of balancing freedom of commercial operation against the inherent risks of pathogen transfer in traded animals, animal products, or any other vehicles for transmission (Boqvist et al., 2014). Beyond the most self-evident pathways (e.g., shipment of live pigs, semen, or unprocessed animal products), most potential scenarios for pathogen spread at the local and international level might reasonably be deemed to have low probability.

Low risks that are borne widely are among the most challenging problems in population health. For example, the popular contention that the US food supply is 'failing consumers' is based upon recent CDC estimates of an annual toll of 48 million cases of foodborne disease, including 128,000 hospitalized cases and 3000 fatalities (Scallan et al., 2011a,b). However, assuming these estimates to be valid, they in fact indicate that the food supply is extraordinarily safe. In terms of individual risk, the probability of these adverse outcomes translates to approximately one case per 7100 meals; one hospitalization per 2.7 million meals; and one fatality per 113 million meals. The challenge of managing events of extremely low, but 'non-zero', risk pertains similarly to international trade in animals and animal products, and to biosecurity practices at the individual farm level. For example, an assessment of trade in animals vaccinated for foot and mouth disease concluded that although risk was deemed to be very low 'it is not possible to assert that the risk is zero', and 'a very low level of risk is both *unavoidable* and *acceptable* if such trade is to be conducted' (Garland and de Clercq, 2011). In an era of increasing trade liberalization and trade volume, it is inevitable that if risks were to remain fixed, undesirable events would become more frequent. Analogously at a herd level, assuming fixed biosecurity practices, the steady increases in herd sizes seen in developed countries will translate into a higher temporal frequency of adverse events due to the greater flux of all inputs (animals, semen, feed, water, biologics, personnel, etc.) into farms. This reality is already reflected in the substantial investments in biosecurity in larger swine herds in the USA, that have

* Corresponding author at. 385 ASVM, 1988 Fitch Ave, St. Paul, MN 55418, USA. Fax:+1 6126251210.
E-mail address: davie001@umn.edu

http://dx.doi.org/10.1016/j.prevetmed.2015.08.006
0167-5877/

underpinned the transition to larger herd sizes without substantial negative impact on swine health (Davies, 2012; Alonso et al., 2013).

2. Continuing an unhappy tradition: emergence and evolution of PEDV as a swine pathogen

Including the 2013 introduction of PEDV, over the last three decades the US swine industry has experienced three major disease epidemics (the 2009 HINI influenza introduction is not included as it had minimal clinical impact in the industry). The respective causative agents share some salient features: all are highly host specific viruses; all exhibit relatively rapid rates of mutation; and all appear to have been associated with swine for years to decades before highly pathogenic disease syndromes were manifest. The sudden emergence of apparently novel pathogens is inherently perplexing, and events of interspecies transmission of previously host-limited pathogens are generally viewed to be of major importance (Chan et al., 2013; Gessain and Garcia-Arenal, 2015). The following discussion presents some evidence to support the proposition that the proximate source of the highly pathogenic variants of each of these 3 viruses was the extant swine virome.

The genomic revolution is transforming paradigms of host-agent interaction from simple models of mutual antagonism towards ecosystem models in which microbes play multiple and complex roles in both health and disease (Cadwell, 2015). The global virome comprises 'the most abundant and fastest mutating genetic elements on earth', with the order of 10^{31} 'members' including viruses that infect host cells, viruses infecting non-viral organisms of the host microbiota, and virus-derived elements from chromosomes (Virgin, 2014). It is suggested that to date only about 1% of the global virome has been identified (Mokili et al., 2012), and that cellular host organisms are like 'islands in an ocean of the global virosphere' (Villarreal and Witzany, 2015). In mammals, bacterial cells outnumber mammalian cells by approximately 10-fold, and the number of viral elements may be another order of magnitude higher. (Mokili et al., 2012). Furthermore, the mammalian virome is in a continual state of flux due to rapid evolution of viruses and introduction of viruses from the environment or between species. (Virgin, 2014).

Over almost 3 decades, porcine reproductive and respiratory syndrome (PRRS) has been unrivalled as the most economically devastating disease of swine in the USA, with annual costs estimated to exceed $664 million (Holtkamp et al., 2013). PRRS was first recognized to be a novel clinical entity in the United States of America in 1987, and has subsequently been confirmed in most swine producing countries (Perez et al., 2015). Experimental reproduction of disease to fulfill Koch's postulates was achieved readily with PRRS virus, confirming its role as the primary pathogen in the syndrome (Terpstra et al., 1993). Based on the coincidence of very similar clinical syndromes, as well as similarities in virus morphology and physicochemical characteristics, it was a reasonable assumption that the Lelystad virus (LV) isolated first in Europe (now type 1 PRRS) and the VR2332 virus later isolated in the USA (now type 2 PRRS) would prove to be the same agent. Perhaps the most extraordinary feature in the history of PRRS was the discovery that the two arteriviruses causing the respective epidemics in North America (circa 1987) and Europe (circa 1990) were clearly distinct. The two epidemics, therefore, appear to be independent events, both of undefined origin. Important differences in antigenicity were observed in the first studies to compare the European and North American prototype viruses. Using pig sera from field cases in Europe and North America it was observed that European sera reacted most with the LV isolates, and North American sera reacted most with US isolates (Wensvoort et al., 1992). Substantial differences between the North American PRRS isolates and LV were consistently reported in later sequencing studies (Mardassi et al., 1994; Murtaugh et al., 2010), and the latter authors considered the genetic differences were consistent with both the biological commonalities and the serological disparities of the two prototype viruses.

Increasingly sophisticated tools of nucleotide sequencing and phylogenetic analysis have been used to investigate the phylogeny and evolution of PRRS viruses. Although estimates of time to most recent common ancestor vary widely, most studies point to divergence of the prototype viruses at least a century before the emergence of the clinical syndromes (Forsberg, 2005). Indeed, recent studies estimate that type 1 PRRS viruses found worldwide diverged approximately 100 years ago and appear to have been endemic in several populations without recognition of any clinical disease (Nguyen et al., 2014). The origin of the viruses remains a mystery, and a working hypothesis is that the type 1 and type 2 viruses diversified in separate reservoirs prior to emergence of the clinical disease (Forsberg, 2005). It has been proposed that a monophyletic origin of PRRS is likely on the basis that one speciation event followed by independent radiation on two different continents is more likely than two independent speciation events with convergent evolution culminating in almost simultaneous epidemics on different continents (Murtaugh et al., 2010). If true, this would imply that non-pathogenic ancestors of PRRS virus were present for perhaps over 100 years in at least some subsets (likely geographically restricted) of the global population of Suidae. However, the earliest serological evidence of pigs being infected with PRRS virus was from 1979 (Carman et al., 1995), some 8 years before the initial reports of the clinical syndrome. Interestingly, although PRRS virus is considered among the most genetically labile viruses, it is highly host specific and has not been found to replicate in any species other than swine (Butler et al., 2014). The genetic lability of PRRS virus appears to play a central role in the difficulties in controlling the disease due to the regular emergence of genetic variants with limited heterologous immunity, and the limited and variable success seen with vaccination (Kappes and Faaberg, 2015; Perez et al., 2015; Wang et al., 2015a).

Porcine circovirus (PCV), a single stranded DNA virus with a circular genome, is the smallest virus known to replicate in mammalian cells (Allan et al., 2012). The two major variants of porcine circoviruses, termed PCV1 and PCV2, share 83% homology in the ORF1 gene but PCV1, originally discovered as a cell culture contaminant, has never been associated with significant clinical disease in pigs (Allan et al., 2012; Xiao et al., 2015). In contrast, PCV2 emerged to be a major pathogen of swine in most swine producing countries. The natural history of PCV2 'from an inoffensive virus to a devastating disease' was recently reviewed in detail (Segales et al., 2013). The first known outbreak of clinical disease linked to PCV2 occurred in 1991 in Saskatchewan, Canada (Ellis, 2014), and initially only sporadic disease was observed. In 1997 severe outbreaks of PCV2 associated disease (PCVAD) were reported in Europe, and similarly severe disease occurred somewhat later (2004–2006) in the USA and Canada (Segales et al., 2013). Although DNA viruses typically have slower mutation rates than RNA viruses (Sanjuan et al., 2010), mutation rates are inversely related to genome size and single stranded DNA viruses appear to have substitution rates approximating those of RNA viruses of similar size (Duffy et al., 2008). The nucleotide substitution rate of PCV2 ($\sim 1.2 \times 10^{-}3$ substitutions/site/year) was the greatest observed in a DNA virus (Firth et al., 2009), and genetic variation appears to have played a central role in the evolution of PCV2 as a pathogen. Within PCV2, 4 clades (PCV2a, PCV2b, PCV2c, PCV2d) have now been delineated, and evidence suggests rapid and ongoing shifts in the global distribution of genotypes over the last 20 years (Xiao et al., 2015). Most notably, the shift from a predominance of PCV2a to PCV2b was temporally

associated with the emergence of severe clinical PCVAD in many countries. However, there is now some indication that the PCV2d clade is becoming increasingly prevalent globally (Xiao et al., 2015). Unlike PRRS virus, the introduction of PCV2 vaccines was remarkably effective in controlling PCVAD. This confirmed the previously uncertain primary role of PCV2 in these clinical syndromes, and almost universal adoption of vaccination in affected industries has the potential to influence the future evolution of the virus (Segales et al., 2013; Ellis, 2014; Xiao et al., 2015).

Again akin to PRRS, the collective epidemiological evidence indicates that PCV2 viruses were likely widespread among the global pig population for at least several decades before the pandemic of severe clinical disease (Jacobsen et al., 2009; Segales et al., 2013). Retrospective studies provide evidence that the virus occurred in pigs as early as 1962, and it was first documented in association with systemic disease of pigs in 1985, over a decade prior to the first epidemics of severe PCVAD (Jacobsen et al., 2009; Segales et al., 2013). Although PCV2 was not thought to have natural hosts other than pigs, there is a very recent report of PCV2 isolation from buffalo in China (Zhai et al., 2014), and mice can be infected experimentally (Wang et al., 2015b). However, the evidence overall indicates a high degree of host specificity for PCV2 virus, including the absence of zoonotic risk (Burbelo et al., 2013).

Unlike PRRS and PCV2, which were previously unknown agents, the alphacoronavirus PEDV is a familiar swine pathogen that has increased in geographical range and clinical severity. The clinical syndrome of porcine epidemic diarrhea was initially observed in feeder pigs and fattening swine in England in 1971, and then later in suckling pigs in the UK and Europe by 1978 when the causal coronavirus was identified (Chasey and Cartwright, 1978; Pensaert and de Bouck, 1978). Although PEDV was associated with some severe outbreaks of disease in Europe, over time it decreased in importance and has only been sporadically reported as a cause of significant clinical disease. In contrast, severe outbreaks of PEDV have occurred in Asia (Japan, China, South Korea and Thailand) since the mid 1990s (Saif et al., 2012). Notably, outbreaks have been very severe in China since 2010, which has been attributed to the emergence of more virulent strains of the virus (Chen et al., 2014). Prior to 2013, PEDV was unknown in the western hemisphere, but over the course of approximately one year PEDV was identified for the first time in the USA, Canada, Mexico, Peru, Colombia, and the Dominican Republic. In addition, outbreaks of more severe clinical disease were observed in some Asian countries from 2013 (Park et al., 2014). Phylogenetic analysis indicates the viruses isolated in the Western Hemisphere are closely related to viruses in China, which is considered the most likely source of introduction to the US. However, the routes of the introductions to the USA and other countries remain unexplained. A recent phylogeographic analysis of 219 PEDV isolates from Asia distinguished two clades designated as 'classical' (clustering with the original European isolates) and 'pandemic' (Sun et al., 2015). Based on the analysis, the authors postulated that the pandemic viruses in Asia likely originated in Korea, which was the location of the oldest virus in this group (1999), then spread into Japan, Thailand and China. Subsequently, pandemic strains emerging in Korea after 2013 appear to have originated from a Chinese variant (Sun et al., 2015). Coronaviruses, notably the zoonotic SARS the MERS viruses, have had a high profile among emerging diseases in several species (Borucki et al., 2013; Graham et al., 2013), and the genetic plasticity of PEDV appears to have played a major role in its transition from a relatively minor and localized pathogen to a major concern for global swine production.

In the 'one health' era, interspecies transmission of pathogens holds the center stage of scientific and public interest. However, the intensive systems of single species food animal production which now predominate in developed countries are arguably more likely to favor the emergence of host specific pathogens (Davies, 2012; Harding, 2014). A striking parallel in the histories of PRRS, PCV2, and PEDV, is that considerable periods passed from the time the viruses were first found in swine until the advent of pandemics of severe disease. An analogous example in human health is the emergence of AIDS associated with HIV-1 and HIV-2 viruses, where current opinion is that the interspecies transmission events of the viruses occurred many decades prior to the recognition of the disease (Sharp and Hahn, 2011). More broadly, it is becoming recognized in both plant and animal systems that cross-species transmission of viruses is followed by complex processes of host adaptation that may have varied outcomes ranging for inapparent infections to severe disease. One study of the fecal virome of pigs reported that 99% percent of viral sequences were related to RNA virus families of the Picornaviridae, Astroviridae, Coronaviridae, and Caliciviridae, and 1% were related to the small DNA virus families Circoviridae, and Parvoviridae (Shan et al., 2011). The porcine RNA viruses identified included kobuviruses, astroviruses, enteroviruses, sapoviruses, sapeloviruses, coronaviruses, bocaviruses, and teschoviruses. Other reports similarly attest to the diversity of the swine virome, including the presence of previously undescribed viruses (Lager et al., 2012 Zhang et al., 2014; Dumarest, et al., 2015). Against this vast, diverse and dynamic backdrop of viral evolution in pigs, the emergence of 3 highly pathogenic viruses over 25 years can be considered extremely rare events, but probably provides a reasonable estimate of what we should anticipate into the future. It is also likely that features of modern swine production including globalization, intensification and extensive movement of pigs have contributed to the success of these agents in expanding their geographic ranges (Murtaugh, et al., 2010; Ayudhya, et al., 2012; Davies, 2012).

Although influenza viruses pose an imminent and perpetual threat for disease emergence from interspecies transmission, the discussion above points to the likelihood that future 'new' viruses causing significant disease in swine will emerge from currently recognized or unrecognized 'orphan' viruses among the extant swine virome. This paradigm presents challenges to national and international animal health authorities with respect to developing models for surveillance and response to emerging diseases that are not readily managed within current norms of regulatory control. As novel agents PRRS and PCV2 were not listed among transboundary diseases of concern, hence there was a vacuum of regulatory authority for managing the diseases at the national or international levels. Similarly, despite being a recognized swine pathogen for decades, as well as reports of severe clinical outbreaks in Asia, the profile of PED virus as a pathogen had not triggered proactive regulatory contingencies at any level. This led, in the face of the outbreak in the Western Hemisphere, to uncertainty and some finger pointing about what the appropriate regulatory responses should entail. In a globalized environment, one can argue that a more sensitive and proactive contingency plan will be required to detect and limit virulent emergent pathogens and thereby avoid pandemic losses on the scale that has occurred with these recent viruses. A more sensitive infrastructure will have costs and impacts that will not be equally shared, especially with respect to trade and market access. Also, it must be recognized that perhaps a majority of 'events of concern' about disease emergence will not presage a pending epidemic. However, the frequency and impact of emerging viral diseases in swine has been such that it demands active consideration of how the inevitable future event should be managed.

3. The baby and the bathwater: feeding products of swine origin

A role for contaminated feed ingredients in the transboundary spread of PEDv, and its subsequent propagation within countries,

has been speculated since the original cases in the USA (Alumbaugh, 2014). Early cases of PEDV in Canada linked to a common feed source led to the recall of swine feed containing spray-dried plasma proteins (SDPP), and recommendations to exclude all products of porcine origin from feed (Byrne, 2014; Pasick, et al., 2014). Field investigations (Dee et al., 2014) and growing anecdotal evidence implicating feed sources in some PEDv outbreaks markedly altered swine feeding practices in the USA, particularly the use of products of porcine origin (e.g., rendered products, SDPP, and hydrolyzed protein products). These precautionary decisions were driven by the economic consequences of introducing PEDV to sow farms, but were made in a virtual vacuum of objective data on the risk of PEDV introduction via feed. On May 6, 2014, the European Commission announced precautionary measures that pig blood products imported for use in pig feed must have been treated at 80 °C and stored for 6 weeks at room temperature due to perceived risks of PEDV. Such changes in feeding strategies add cost to production and disrupt markets, augmenting the impact of PEDv beyond direct production losses. In delivering the Tom Alexander Lecture at the International Pig Veterinary Society meeting in July 2014, Dr. John Harding provided a comprehensive overview of concerns about emerging diseases in modern swine production (Harding, 2014). This included some strong and radical recommendations for altering industry structure and operations. Among them were recommendations that feed industries globally 'discontinue the importation of animal protein destined for any livestock or pet food, and to find alternative sources of protein suitable for nursery pigs', and that all national governments 'ban the feeding of rendered pigs and pig by-products back to pigs.'

For feed to be a vehicle of pathogen transmission, it must become contaminated with an infectious agent that can survive the journey through feed manufacturing and distribution to be ingested in sufficient dose to cause infection. As omnivores, the ability of swine to convert diverse food sources into high quality protein and fat was central to their domestication and still drives swine nutrition today (Stein and Shurson, 2009). Exposure risk to physical, chemical or biological hazards via ingestion is self-evident and most developed countries regulate animal feeding due to concerns about introduction of foreign animal pathogens via feed. In the USA, the Swine Health Protection Act (1980) regulates feeding of 'garbage' (defined as waste derived from meat or other animal materials) to pigs, which is legal only after heating the materials to 212° F for 30 min, and under license. However, processed products of animal origin are legal and valuable components of swine diets, notably rendered products, spray dried porcine plasma (SDPP), hydrolyzed proteins that are byproducts of heparin extraction, and pet food byproducts (Cromwell, 2006; Jablonski, et al., 2006; Peace, et al., 2011; Myers, et al., 2014). The Animal Feed Safety System (AFSS) of the Food and Drug Administration (FDA) approves feed additives; oversees regulatory compliance pertaining to feed manufacturing, labeling, storage, and distribution; and acts to remove unsafe feed from the marketplace. AFSS has historically focused on specific issues such as residues from medicated feeds, bovine spongiform encephalopathy (BSE), and *Salmonella*. International Codex Alimentarius guidelines and the US feed industry's voluntary 'Safe Feed/Safe Food' program focus mostly on chemical hazards and only BSE, *Salmonella*, *Brucella*, and some parasites are specifically identified as biological hazards of concern in animal feed (Anon., 2010; Food and Drug Administration, 2014). The heavy emphasis on chemical rather than biological hazards common to these programs reflects, with well-known exceptions, the relative unimportance of feed in transmission of most biological hazards, particularly viruses. Prior to the emergence of PEDV in North America, there was a paucity of reports implicating animal feed as a mode of transmission of swine viruses (Kim, et al., 2008).

The presence of endemic pathogens in raw materials of porcine origin is inevitable, and substantial research has been done to establish the safety of rendered and spray-dried products destined for animal feed (Polo et al., 2005; Franco, 2006; Pujols et al., 2011). Historically, the paucity of published reports of disease outbreaks linked to swine feed in the USA indicates that existing procedures for mitigating risk have delivered an acceptable level of protection over an extended period. However, investigations of the first cases of PEDV identified in Canada, and of a unrelated outbreak in the USA, implicated contaminated feed ingredients and feed as a vehicles of transmission (Dee, et al., 2014; Pasick, et al., 2014). SDPP associated with the Canadian outbreak that was imported from the USA tested positive for PEDV RNA. Bioassays were performed using both SDPP and feed containing 6% SDPP by administering 5 g of material in 50 ml of suspension per pig. No infection occurred in the pigs receiving complete feed, but PEDV infection confirmed in the pigs receiving SDPP and also in pigs placed in contact with them 11 days after exposure (Pasick, et al., 2014). In addition, among the affected herds a dose-response relationship was observed with the inclusion rate of SDPP, (O'Sullivan et al., 2015) with an attack rate of approximately 30% in herds in the highest exposure category of 3 to–6% SDPP (Pascale Aubry, personal communication). In contrast, industry data indicate that large amounts (corresponding to the consumption by 3.4–4 million pigs) of PCR positive SDPP (mean Ct = 31.1) were exported and fed to pigs in western Canada and Brazil without PEDV outbreaks occurring (Crenshaw, et al., 2014).

Many North American veterinarians and producers have adopted the precautionary approach advocated by Harding to withhold all materials of porcine origin from swine diets. An alternative approach is to apply risk assessment methods to integrate available data on processing methods and the characteristics of the virus to attempt to quantify risks, their associated uncertainties and economic implications, and data gaps that should be addressed in future research. Our group at the University of Minnesota conducted a risk assessment of the transmission of PEDv in feed ingredients of porcine origin. (Sampedro, et al., 2015) Estimated D-values (time need for a 1-log reduction of virus at a given temperature) based on recent experimental studies at the University of Minnesota were used to assess the impact on PEDV survival of thermal inactivation as employed in the respective processes (rendering, spray-drying, hydrolysates). It is important to note that D-values are temperature and matrix specific, and the experimental conditions were not identical to commercial conditions. Although no data were available on raw material contamination entering the rendering and hydrolysate processes, the large log reductions predicted for thermal inactivation with the time-temperature combinations employed in these processes indicated negligible risk of PEDV survival, even at high levels of contamination of raw materials.

Much shorter time-temperature profiles are employed in spray-drying, and assessment of thermal inactivation alone predicted potential survival of PEDV under some assumptions regarding initial virus viability. However, it is recognized that observations on thermal resistance alone do not accurately predict survival of organisms during spray-drying (Licari and Potter, 1970; Ghandi, et al., 2012). Modeling was also performed using recent experimental data on PEDV inactivation in laboratory scale spray dryers (Gerber, et al., 2014; Pujols and Segales, 2014) and predicted negligible survival of PEDV during the spray-drying process across a range of assumptions regarding initial virus viability. However, one source of uncertainty is that laboratory scale processes do not exactly reflect the range of conditions in commercial scale spray dryers. The complexity of 'scaling up' of spray-drying processes is well recognized and differences in the physical environment surrounding particles and their thermohydric profiles vary between laboratory, pilot, and commercial scales (Thybo, et al., 2008). Also,

variability in spray-drying conditions or inconsistency in the processes could potentially lead to incomplete viral inactivation on occasions (Gerber, et al., 2014). In conclusion, the apparently uneventful history of feeding SDPP to pigs over the last two decades, together with currently available data suggest that the risk of PEDV survival in porcine plasma under current industry conditions of spray drying and storage is extremely low, but non-zero. However, data limitations on several important aspects would need to be addressed to reach more robust conclusions (Sampedro, et al., 2015).

4. The dilemma of managing low risks

The identification of a non-zero, but likely very low, risk of PEDV transmission via feed represents a dilemma of low individual risk but high collective risk that is analogous to the problem of risk management in the human food supply. Bioassay experiments used to assess PEDV viability in SDPP or feed have to date used small (4–40) numbers of animals per group, typically with single or double exposure of a small amount (0.9–8 g) of feed or ingredient (Gerber, et al., 2014; Pasick, et al., 2014). In contrast, under modern commercial conditions weaned pigs in a 2500 head facility might consume 50 kg of SDPP in a week (0.4 kg daily feed intake; 5% SDPP in feed). Notably, in the Canadian outbreak of PEDV in early 2014, approximately 70% of herds receiving the suspected ingredient in the high exposure group (3–6% of SDPP) did not become infected. This implies that risk at the individual pig level was extremely low and unlikely to be reproduced with complete feed in small bioassay studies. This is not an unprecedented problem, as infection of animals (particularly young chicks) with *Salmonella* can occur at levels of feed contamination that are below the limit of detection, making the conceptually appealing recommendation for '*Salmonella* free' feed problematic under commercial conditions (Davies, et al., 2004).

Returning to the question of risk management, the complete withdrawal of all products of porcine origin from swine diets seems a sound recommendation when viewed through the narrow prism of swine health. However, public scrutiny of meat industries is increasingly focused on many other issues, including the environmental impact of meat consumption (Sabate and Soret, 2014; Alsaffar, 2015). All constraints on diets will introduce costs, and the diverse processes used to produce the range of feed ingredients of porcine origin will not present equivalent risk profiles. Therefore, there is room for a more nuanced discussion of the relative merits of withdrawing specific feed ingredients from diets. The long history of feeding pigs with protein and fat products derived from rendering has yielded remarkably little angst about animal health, with possible exception of *Salmonella* from the food safety perspective. As yet there is no concrete or circumstantial evidence implicating rendered products in the spread of PEDV. In the USA, livestock and poultry account for over half of the use of protein products, and 35% of the fat products, from the rendering industry (Sampedro, et al., 2015), and the use of these recycled nutrients makes a valuable contribution to reducing the environmental impact of meat production.

An arguably extreme example of the consequences of banning animal byproducts can be found in estimates of costs of the BSE epidemic in Europe. The largest component of cost (>50%) was due to the withdrawal of animal proteins from the animal feed chain, estimated to be approximately 1 billion Euro in Germany alone (Probst, et al., 2013). An analysis of the 'cost of the precautionary principle' in the Netherlands estimated the cost-effectiveness of all BSE measures in the Netherlands ranged from 4.3 million euros per life year saved in 2002 to 17.7 million euros in 2005 (Benedictus, et al., 2009). Additionally, one analysis linked deforestation of Brazilian rainforest to greater soybean demand in the EU due to the BSE preventive measures (Elferink, et al., 2007). The point is not to debate the wisdom of the precautionary principle in specific circumstances, but to propose that a blanket and global ban on use of ingredients of porcine origin in swine feed could have substantial negative economic and environmental consequences that need to be objectively assessed. As stated by Boqvist et al. (2014), 'the complexity of science means that simple solutions to challenges provided by contagious animal diseases are rare. Cost–benefit analyses are very important for policy makers as a basis for deciding on cost effective control measures. Such analyses are not straightforward and depend on data availability and quality, as well as decisions on which costs should be included and how costs are calculated' (Boqvist, et al., 2014). As we shift into the post epidemic phase of PEDV in North America, there is a challenge to integrate information that is now accumulating rapidly to underpin sound policies for risk management from the herd to the international level. This should include more comprehensive evaluation of the relative importance of different pathways of PEDV transmission among farms, as well as cost-benefit of managing feed related risks (both from ingredients and cross contamination) in relation to the nutritional value of respective ingredients.

References

Allan, G., Krakowka, S., Ellis, J., Charreyre, C., 2012. Discovery and evolving history of two genetically related but phenotypically different viruses, porcine circoviruses 1 and 2. Virus Res. 164, 4–9.

Alonso, C., Davies, P.R., Polson, D., Dee, S.A., Lazarus, W., 2013. Financial implications of installing air filtration systems to prevent PRRSV infection in large sow herds. Prev. Vet. Med. 111, 268-77-277.

Alsaffar, A.A., 2015. Sustainable diets: the interaction between food industry, nutrition, health and the environment. Food Sci. Technol. Int.

Alumbaugh J., Feed ingredients potentially involved in PED transmission. Pork Network. Available: http://www.porknetwork.com/editorial/joann-alumbaugh/Feed-ingredients-potentially-involved-in-PED-transmission-247055461.html. Accessed: September 2014.

Anon, 2010. Good Practices for the Feed Industry: Implementing the Codex Alimentarius Code of Practice on Good Animal Feeding. FAO Animal Production and Health Manual No. 9, Rome.

Ayudhya, S.N., Assavacheep, P., Thanawongnuwech, R., 2012. One world–one health: The threat of emerging swine diseases. an Asian perspective. Transbound Emerg. Dis. 59 (Suppl. 1), 9–17.

Benedictus, A., Hogeveen, H., Berends, B.R., 2009. The price of the precautionary principle: cost-effectiveness of BSE intervention strategies in the Netherlands. Prev. Vet. Med. 89, 212–222.

Boqvist, S., Dekker, A., Depner, K., Grace, D., Hueston, W., Stark, K.D., Sternberg Lewerin, S., 2014. Contagious animal diseases: the science behind trade policies and standards. Vet. J. 202, 7–10.

Borucki, M.K., Allen, J.E., Chen-Harris, H., Zemla, A., Vanier, G., Mabery, S., Torres, C., Hullinger, P., Slezak, T., 2013. The role of viral population diversity in adaptation of bovine coronavirus to new host environments. PLoS One 8, e52752, e52752.

Burbelo, P.D., Ragheb, J.A., Kapoor, A., Zhang, Y., 2013. The serological evidence in humans supports a negligible risk of zoonotic infection from porcine circovirus type 2. Biologicals 41, 430–434.

Butler, J.E., Lager, K.M., Golde, W., Faaberg, K.S., Sinkora, M., Loving, C., Zhang, Y.I., 2014. Porcine reproductive and respiratory syndrome (PRRS): an immune dysregulatory pandemic. Immunol. Res. 59, 81–108.

Byrne, J., PED virus: Industry and academics investigate feed transmission route. Feed Navigator May 13, 2014. http://www.feednavigator.com/R-D/PED-virus-industry-and-academics-investigate-feedtransmission-route

Cadwell, K., 2015. The virome in host health and disease. Immunity 42, 805–813.

Carman, S., Sanford, S.E., Dea, S., 1995. Assessment of seropositivity to porcine reproductive and respiratory syndrome (PRRS) virus in swine herds in Ontario–1978 to 1982. Can. Vet. J 36, 776–777.

Chan, J.F., To, K.K., Tse, H., Jin, D.Y., Yuen, K.Y., 2013. Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiol. 21, 544–555.

Chasey, D., Cartwright, S.F., 1978. Virus-like particles associated with porcine epidemic diarrhoea. Res. Vet. Sci. 25, 255–256.

Chen, Q., Li, G., Stasko, J., Thomas, J.T., Stensland, W.R., Pillatzki, A.E., Gauger, P.C., Schwartz, K.J., Madson, D., Yoon, K.J., Stevenson, G.W., Burrough, E.R., Harmon, K.M., Main, R.G., Zhang, J., 2014. Isolation and characterization of porcine epidemic diarrhea viruses associated with the 2013 disease outbreak among swine in the United States. J. Clin. Microbiol. 52, 234–243.

Crenshaw, J.D., Campbell, J.M., Polo, J., 2014. Analysis of spray dried porcine plasma (SDPP) produced in Brazil and western Canada confirm negative porcine epidemic diarrhea virus (PEDV) status of pigs in these regions. In: Proceedings, Allen D. Leman Swine Conference, September 13,16, 2014, St. Paul, Minnesota, 40:14 (abstr.).
Cromwell, G.L., 2006. Rendered products in swine nutrition. In: Meeker, D.L. (Ed.), Essential Rendering. National Renderers Association.
Davies, P.R., 2012. One world, one health: The threat of emerging swine diseases. a North American perspective. Transbound Emerg. Dis. 59, 18–26.
Davies, P.R., Scott Hurd, H., Funk, J.A., Fedorka-Cray, P.J., Jones, F.T., 2004. The role of contaminated feed in the epidemiology and control of *Salmonella enterica* in pork production. Foodborne Pathog. Dis. 1, 202–215.
Dee, S., Clement, T., Schelkopf, A., Nerem, J., Knudsen, D., Christopher-Hennings, J., Nelson, E., 2014. An evaluation of contaminated complete feed as a vehicle for porcine epidemic diarrhea virus infection of naive pigs following consumption via natural feeding behavior: proof of concept. BMC Vet. Res. 10, 176.
Duffy, S., Shackelton, L.A., Holmes, E.C., 2008. Rates of evolutionary change in viruses: patterns and determinants. Nat. Rev. Genet. 9, 267–276.
Dumarest, M., Muth, E., Cheval, J., Gratigny, M., Hebert, C., Gagnieur, L., Eloit, M., 2015. Viral diversity in swine intestinal mucus used for the manufacture of heparin as analyzed by high-throughput sequencing. Biologicals 43, 31–36.
Elferink, E.V., Nonhebel, S., Uiterkamp, A.J.M.S., 2007. Does the Amazon suffer from BSE prevention? Agric. Ecosyst. Environ. 120, 467-469-469.
Ellis, J., 2014. Porcine circovirus: a historical perspective. Vet. Pathol. 51, 315–327.
Firth, C., Charleston, M.A., Duffy, S., Shapiro, B., Holmes, E.C., 2009. Insights into the evolutionary history of an emerging livestock pathogen: porcine circovirus 2. J. Virol. 83, 12813–12821.
Food and Drug Administration, 2014. Animal feed safety system. http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AnimalFeedSafetySystemAFSS/UCM277673.pdf
Forsberg, R., 2005. Divergence time of porcine reproductive and respiratory syndrome virus subtypes. Mol. Biol. Evol. 22, 2131–2134.
Franco, D.A., 2006. The rendering industry's role in feed and food safety. In: Meeker, D.L. (Ed.), Essential Rendering. National Renderers Association, pp. 53–69.
Garland, A.J., de Clercq, K., 2011. Cattle, sheep and pigs vaccinated against foot and mouth disease: does trade in these animals and their products present a risk of transmitting the disease? Rev. Sci. Tech. 30, 189–206.
Gerber, P.F., Xiao, C.T., Chen, Q., Zhang, J., Halbur, P.G., Opriessnig, T., 2014. The spray-drying process is sufficient to inactivate infectious porcine epidemic diarrhea virus in plasma. Vet. Microbiol. 174, 86–92.
Gessain, A., Garcia-Arenal, F., 2015. Editorial overview: emerging viruses: interspecies transmission. Curr. Opin. Virol. 10, v–viii.
Ghandi, A., Powell, I.B., Howes, T., Chen, X.D., Adhikari, B., 2012. Effect of shear rate and oxygen stresses on the survival of lactococcus lactis during the atomization and drying stages of spray drying: a laboratory and pilot scale study. J. Food Eng. 113, 194–200.
Graham, R.L., Donaldson, E.F., Baric, R.S., 2013. A decade after SARS: strategies for controlling emerging coronaviruses. Nat. Rev. Microbiol. 11, 836–848.
Harding, J.C.S., 2014. Accountabilities in the age of transboundary and emerging porcine diseases. In: 1-12. 23rd International Pig Veterinary Society Congress, Cancun, Mexico; June 8–11, pp. 1–12.
Holtkamp, D.J., Kliebenstein, J.B., Neumann, E.J., Zimmerman, J.J., Rotto, H., Yoder, T.K., Wang, C., Yeske, P., Mowrer, C., Haley, C., 2013. Assessment of the economic impact of porcine reproductive and respiratory syndrome virus on U. S. pork producers. Swine Health Prod. 21, 72–84.
Jablonski, E.A., Jones, R.D., Azain, M.J., 2006. Evaluation of pet food by-product as an alternative feedstuff in weanling pig diets. J. Anim. Sci. 84, 221–228.
Jacobsen, B., Krueger, L., Seeliger, F., Bruegmann, M., Segales, J., Baumgaertner, W., 2009. Retrospective study on the occurrence of porcine circovirus 2 infection and associated entities in northern Germany. Vet. Microbiol. 138, 27–33.
Kappes, M.A., Faaberg, K.S., 2015. PRRSV structure, replication and recombination: Origin of phenotype and genotype diversity. Virology 479-480, 475–486.
Kim, B., Song, J.Y., Tark, D.S., Lim, S.I., Choi, E.J., Kim, J., Park, C.K., Lee, B.Y., Wee, S.H., Bae, Y.C., Lee, O.S., Kwon, J.H., Kang, W.C., Kim, T.Y., Kim, J.H., Lee, J.H., Kang, M.I., 2008. Feed contaminated with classical swine fever vaccine virus (LOM strain) can induce antibodies to the virus in pigs. Vet. Rec. 162, 12–17.
Lager, K.M., Ng, T.F., Bayles, D.O., Alt, D.P., Delwart, E.L., Cheung, A.K., 2012. Diversity of viruses detected by deep sequencing in pigs from a common background. J. Vet. Diagn. Invest. 24, 1177–1179.
Licari, J.J., Potter, N.N., 1970. *Salmonella* survival during spray drying and subsequent handling of skimmilk powder. I. *Salmonella* enumeration. J. Dairy Sci. 53, 865–870.
Mardassi, H., Mounir, S., Dea, S., 1994. Identification of major differences in the nucleocapsid protein genes of a Quebec strain and European strains of porcine reproductive and respiratory syndrome virus. J. Gen. Virol. 75, 681–685.
Mokili, J.L., Rohwer, F., Dutilh, B.E., 2012. Metagenomics and future perspectives in virus discovery. Curr. Opin. Virol. 2, 63–77.
Murtaugh, M.P., Stadejek, T., Abrahante, J.E., Lam, T.T.Y., Leung, F.C.-, 2010. The ever-expanding diversity of porcine reproductive and respiratory syndrome virus. Virus Res. 154, 18–30.
Myers, A.J., Goodband, R.D., Tokach, M.D., Dritz, S.S., DeRouchey, J.M., Nelssen, J.L., 2014. The effects of porcine intestinal mucosa protein sources on nursery pig growth performance. J. Anim. Sci. 92, 783–792.
Nguyen, V.G., Kim, H.K., Moon, H.J., Park, S.J., Chung, H.C., Choi, M.K., Park, B.K., 2014. A bayesian phylogeographical analysis of type 1 porcine reproductive and respiratory syndrome virus (PRRSV). Transbound Emerg. Dis. 61, 537–545.
O'Sullivan, T., Poljak, Z., Friendship, R., Dewey, C., 2015. Investigation of factors that led to emergence of PEDV through feed during early phase of Canadian outbreak. In: Proceedings, 7th International Symposium on Emerging and Re-emerging Pig Diseases, Kyoto , Japan, June 21–24, #O-21.
Park, S., Kim, S., Song, D., Park, B., 2014. Novel porcine epidemic diarrhea virus variant with large genomic deletion, South Korea. Emerg. Infect. Dis. 20, 2089–2092.
Pasick, J., Berhane, Y., Ojkic, D., Maxie, G., Embury-Hyatt, C., Swekla, K., Handel, K., Fairles, J., Alexandersen, S., 2014. Investigation into the role of potentially contaminated feed as a source of the first-detected outbreaks of porcine epidemic diarrhea in Canada. Transbound Emerg. Dis. 61, 397–410.
Peace, R.M., Campbell, J., Polo, J., Crenshaw, J., Russell, L., Moeser, A., 2011. Spray-dried porcine plasma influences intestinal barrier function, inflammation, and diarrhea in weaned pigs. J. Nutr. 141, 1312–1317.
Pensaert, M.B., de Bouck, P., 1978. A new coronavirus-like particle associated with diarrhea in swine. Arch. Virol. 58, 243–247.
Perez, A., Davies, P., Goodell, C., Holtkamp, D., Mondaca, E., Poljak, Z., Tousignant, S., Valdes-Donoso, P., Zimmerman, J., Morrison, R., 2015. Review of literature for epidemiology and control of porcine reproductive 1 and respiratory syndrome virus (PRRSV) in North America: lessons learned and knowledge gaps. J. Am. Vet. Med. Assoc. 246, 1304–1317.
Pitkin, A., Otake, S., Dee, S., 2009. Biosecurity protocols for the prevention of spread of porcine reproductive and respiratory syndrome virus. Swine Disease Eradication Center, University of Minnesota. St. Paul, MN http://www.cvm.umn.edu/sdec/prod/groups/cvm/@pub/@cvm/@respond/documents/content/cvm_content_445334.pdf
Polo, J., Quigley, J.D., Russell, L.E., Campbell, J.M., Pujols, J., Lukert, P.D., 2005. Efficacy of spray-drying to reduce infectivity of pseudorabies and porcine reproductive and respiratory syndrome (PRRS) viruses and seroconversion in pigs fed diets containing spray-dried animal plasma. J. Anim. Sci. 83, 1933–1938.
Probst, C., Gethmann, J.M., Heuser, R., Niemann, H., Conraths, F.J., 2013. Direct costs of bovine spongiform encephalopathy control measures in Germany. Zoonoses Public Health 60, 577–595.
Pujols, J., Lorca-Oro, C., Diaz, I., Russell, L.E., Campbell, J.M., Crenshaw, J.D., Polo, J., Mateu, E., Segales, J., 2011. Commercial spray-dried porcine plasma does not transmit porcine circovirus type 2 in weaned pigs challenged with porcine reproductive and respiratory syndrome virus. Vet. J. 190, e16–e20.
Pujols, J., Segales, J., 2014. Survivability of porcine epidemic diarrhea virus (PEDV) in bovine plasma submitted to spray drying processing and held at different time by temperature storage conditions. Vet. Microbiol. 174, 427–432.
Sabate, J., Soret, S., 2014. Sustainability of plant-based diets: back to the future. Am. J. Clin. Nutr. 100 (Suppl 1), 476S–482S.
Saif, L.J., Pensaert, M., Sestak, K., Yeo, S.G., Jung, K., 2012. Coronaviruses. In: Zimmerman, J.J. (Ed.), Diseases of Swine. Wiley-Blackwell, Ames, IA, pp. 501–524.
F. Sampedro, T. Snider, I. Bueno, J. Bergeron, P. Urriola, P. Davies, Risk assessment of feed ingredients of porcine origin as vehicles for transmission of porcine epidemic diarrhea virus. 2015; http://research.pork.org/FileLibrary/ResearchDocuments/14-164-DAVIES-UofMN.pdf
Sanjuan, R., Nebot, M.R., Chirico, N., Mansky, L.M., Belshaw, R., 2010. Viral mutation rates. J. Virol. 84, 9733–9748.
Scallan, E., Griffin, P.M., Angulo, F.J., Tauxe, R.V., Hoekstra, R.M., 2011a. Foodborne illness acquired in the United States–unspecified agents. Emerg. Infect. Dis. 17, 16–22.
Scallan, E., Hoekstra, R.M., Angulo, F.J., Tauxe, R.V., Widdowson, M.A., Roy, S.L., Jones, J.L., Griffin, P.M., 2011b. Foodborne illness acquired in the United States–major pathogens. Emerg. Infect. Dis 17, 7–15.
Segales, J., Kekarainen, T., Cortey, M., 2013. The natural history of porcine circovirus type 2: from an inoffensive virus to a devastating swine disease? Vet. Microbiol. 165, 13–20.
Shan, T., Li, L., Simmonds, P., Wang, C., Moeser, A., Delwart, E., 2011. The fecal virome of pigs on a high-density farm. J. Virol. 85, 11697–11708.
Sharp, P.M., Hahn, B.H., 2011. Origins of HIV and the AIDS pandemic. Cold Spring Harb. Perspect. Med. 1, a006841.
Stein, H.H., Shurson, G.C., 2009. Board-invited review: the use and application of distillers dried grains with solubles in swine diets. J. Anim. Sci. 87, 1292–1303.
Sun, M., Ma, J., Wang, Y., Wang, M., Song, W., Zhang, W., Lu, C., Yao, H., 2015. Genomic and epidemiological characteristics provide new insights into the phylogeographical and spatiotemporal spread of porcine epidemic diarrhea virus in Asia. J. Clin. Microbiol. 53, 1484–1492, http://dx.doi.org/10.1128/JCM.02898-14.
Terpstra, C., Wensvoort, G., Pol, J.M., 1993. Experimental reproduction of porcine epidemic abortion and respiratory syndrome (mystery swine disease) by infection with Lelystad virus - Koch postulates fulfilled. Vet. Quart. 1991, 131–136.
Thybo, P., Hovgaard, L., Lindelov, J.S., Brask, A., Andersen, S.K., 2008. Scaling up the spray drying process from pilot to production scale using an atomized droplet size criterion. Pharm. Res. 25, 1610–1620.
Villarreal, L.P., Witzany, G., 2015. When competing viruses unify: evolution, conservation, and plasticity of genetic identities. J. Mol. Evol. 80, 305–318.
Virgin, H.W., 2014. The virome in mammalian physiology and disease. Cell 157, 142–150.

Wang, X., Marthaler, D., Rovira, A., Rossow, S., Murtaugh, M.P., 2015a. Emergence of a virulent porcine reproductive and respiratory syndrome virus in vaccinated herds in the United States. Virus Res.

Wang, Y., Lu, Y., Liu, D., Wei, Y., Guo, L., Wu, H., Huang, L., Liu, J., Liu, C., 2015b. Enhanced Th1-biased immune efficacy of porcine circovirus type 2 cap-protein-based subunit vaccine when coadministered with recombinant porcine IL-2 or GM-CSF in mice. Appl. Microbiol. Biotechnol. 99, 1155–1163.

Wensvoort, G., de Kluyver, E.P., Luijtze, E.A., den Besten, A., Harris, L., Collins, J.E., Christianson, W.T., Chladek, D., 1992. Antigenic comparison of Lelystad virus and swine infertility and respiratory syndrome (SIRS) virus. J. Vet. Diagn. Invest. 4, 134–138.

Xiao, C.T., Halbur, P.G., Opriessnig, T., 2015. Global molecular genetic analysis of porcine circovirus type 2 (PCV2) sequences confirms the presence of four main PCV2 genotypes and reveals a rapid increase of PCV2d. J. Gen. Virol. 96, 1830–1841.

Zepeda, C., Salman, M., Thiermann, A., Kellar, J., Rojas, H., Willeberg, P., 2005. The role of veterinary epidemiology and veterinary services in complying with the World Trade Organization SPS agreement. Prev. Vet. Med. 67, 125–140.

Zhai, S.L., He, D.S., Qi, W.B., Chen, S.N., Deng, S.F., Hu, J., Li, X.P., Li, L., Chen, R.A., Luo, M.L., Wei, W.K., 2014. Complete genome characterization and phylogenetic analysis of three distinct buffalo-origin PCV2 isolates from China. Infect. Genet. Evol. 28, 278–282.

Zhang, B., Tang, C., Yue, H., Ren, Y., Song, Z., 2014. Viral metagenomics analysis demonstrates the diversity of viral flora in piglet diarrhoeic faeces in China. J. Gen. Virol. 95, 1603–1611.