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

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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

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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

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