

REVIEW ARTICLE

One World – One Health: The Threat of Emerging Swine Diseases. An Asian Perspective

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Southeast Asia; emerging diseases; foot and mouth disease; porcine epidemic diarrhoea; porcine reproductive and respiratory syndrome; swine

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Summary

Owing to the expanding globalization, the trans-boundary spread of an epizootic can easily result from uncontrolled animal movements and human traffic. Foot and mouth disease (FMD) is a major trans-boundary disease in most Asian countries. Its sporadic re-emergence suggests that collaborative FMD control strategies should be uniformly implemented in endemic countries to ensure the overall national herd vaccination coverage, biocontainment when outbreaks occur, and strict biosecurity control of animal movement between countries. Sustained commitments from governments, cooperative diplomatic relationships, and public awareness campaigns are critical to FMD control, to ensure collaboration among veterinarians, traders and farmers throughout Southeast Asia (SEA). Recently, highly pathogenic porcine reproductive and respiratory syndrome (HP-PRRS) and porcine epidemic diarrhoea (PED) spread from China to Southeast Asian countries, causing major economic losses. Foot and mouth disease, HP-PRRS, and PED currently remain endemic and may continue to sporadically re-emerge, owing to inadequate public health management and/or biosecurity failures. Therefore, the risk factors must be identified to better understand the epidemiology of these diseases in an effort to develop effective control measures. International coordination through the establishment of a collaborative network supported by the World Organization for Animal Health (OIE) and the Food and Agriculture Organization (FAO) should be implemented to prevent trans-boundary transmission among countries. This review discusses trans-boundary swine diseases of particular importance to SEA, including FMD, HP-PRRS and PED, with a primary focus on major factors contributing to the spread of these diseases and important control measures, reflecting the impact of globalization on disease control and surveillance.

Introduction

Several viral diseases, including foot-and-mouth disease (FMD), classical swine fever (CSF), and Aujeszky's disease (AD), remain endemic in Asia, especially in Southeast Asia (SEA). Such diseases continue to sporadically re-emerge as a result of biosecurity and/or vaccination failures. Recently, FMD outbreaks in Japan and South Korea had a major impact on the international swine industry

(Seneque, 2011). Classical swine fever continues to cause high mortality in back-yards and small holders, decreasing incomes and food security in many rural Asian villages. Occasionally, the virus spills into industrial farms, causing varying economic loss, depending on herd immune status. Similarly, AD seems currently under control through routine vaccination, but it remains endemic in most of SEA. Affected countries have committed significant financial resources to vaccination and diagnostics

for the prevention and control these infectious swine diseases.

During the past two decades, porcine reproductive and respiratory syndrome (PRRS) (Thanawongnuwech et al., 2004a,b) and porcine circovirus-associated diseases (PCVAD) (Tantilertcharoen et al., 1999) have emerged in a number of Asian countries, possibly introduced via imported breeding stock and semen for artificial insemination. These diseases became endemic owing to previously unrestricted animal movements and biosecurity failures between and within these countries. It should be noted that highly pathogenic PRRS (HP-PRRS), first recognized in China in 2006 (An et al., 2010), has spread to the Philippines (Barrette et al., 2009), Vietnam (Tung et al., 2011), Cambodia (Theary et al., 2011), Lao PDR (Phommachanh et al., 2011), Thailand (Thanawongnuwech, 2011) and most recently to Myanmar (Ling Ling Bo, 2011, personal communication). Similarly, following its first appearance in China in 2004, a Chinese-like strain of porcine epidemic diarrhoea (PED) has become prevalent in Thailand since 2007 (Puranaveja et al., 2009) and in Vietnam since 2009 (Duy et al., 2011).

Factors involved in the transmission within and across borders will be discussed. However, animal movement among neighbouring countries plays a major role in such incidents. These emerging and re-emerging swine diseases provide Asian swine veterinarians with unique challenges in determining more suitable screening diagnostics and acquiring a better understanding of pathogenesis. Changes in herd size and operational systems represent additional challenges to disease control because of the limitations in biosecurity. This manuscript discusses current emerging swine diseases in SEA, including FMD, HP-PRRS and PED, as well as the major factors involved in the spread of these diseases. Critical challenges to control and surveillance are addressed with regard to the impact of globalization on these trans-boundary swine diseases.

Foot and Mouth Disease (FMD)

Foot and mouth disease virus is comprised of seven serotypes with several subtypes that continually evolve and mutate, contributing to its genetic and antigenic variation (Seneque, 2011). Different host species exhibit varying disease susceptibility. Three FMD virus serotypes, O, A, and Asia 1, are endemic in mainland SEA (Abila and Kalpravidh, 2011). Infection with one serotype does not confer cross-immunity to other serotypes.

Southeast Asia, pan-Asia and Cathay ('pig-adapted') strains are three distinct groupings of serotype O that have been identified in Asia. Type O strains were responsible for several epidemics, including the Cathay strain in the Philippines (1994) and Taiwan (1997), Asian/UK epi-

zootics of O pan-Asia (2000–2001), and the Southeast Asia strain in Indochina (1997), and Hong Kong, Japan, and Korea (2009–2010) (Grubman and Baxt, 2004; Seneque, 2011).

Potentially, the most genetically variable FMD serotype, serotype A, is endemic in ruminant populations in Thailand. Sporadic outbreaks have also been reported in Cambodia, Lao PDR, Vietnam and Malaysia (Abila and Kalpravidh, 2011). Serotype Asia 1 is the most antigenically stable among the three endemic serotypes. It was last detected in Myanmar in 2001, Lao PDR in 1999, Malaysia in 1999, Thailand in 1998, Cambodia in 1997 and Vietnam in 1992 (Abila and Kalpravidh, 2011).

Direct contact is a common FMD transmission route, especially for comingling pigs during production stages. Foot and mouth disease virus can be transmitted via infected semen and milk. Transmissions via contaminated non-affected host animals, animal products and wind-borne materials have also been reported, and mechanical vectors include contaminated equipment, motor vehicles and insects. However, epidemiological evidence suggests that carrier animals transported within disease-affected countries and across international borders are often the origin of outbreaks of acute FMD (Sobrino et al., 2001). The carrier state, which can last as long as 3.5 years in cattle, has also been identified in sheep and goats, but not in pigs (Alexandersen et al., 2002). Several outbreaks in southern Thailand and northern Malaysia serve as examples for the spread of FMD from endemic hotspots to neighbouring areas owing to cattle movements. Risk assessments for trans-boundary movement of FMD include environmental factors, religious and cultural practices, disease incidence status, range of farming systems, trans-boundary animal and animal product trade pathways, and national disease control and biosecurity capabilities.

Vaccines play a major role in FMD control, both in endemic and in non-endemic areas, and are also used strategically as an aid for outbreak control and eradication efforts, as neutralizing antibodies appear as early as 7 days and reach maximum titres within 2 weeks after vaccination (Sobrino et al., 2001). However, vaccination with one FMD serotype does not confer cross-protection against other serotypes. In addition, vaccine efficacy may vary among isolates of the same FMD serotype owing to antigenic diversity. It should be noted that, while vaccination may slow an outbreak in swine, it is highly advisable to implement additional control measures, such as pre-emptive culling of in-contact swine herds, as FMD vaccination in pigs may be less effective in comparison to ruminants (Orsel and Bouma, 2009). For decades, Thailand has implemented a mass vaccination strategy using trivalent vaccines produced from local isolates. However,

vaccination is not uniform in most countries, as routine FMD vaccinations are used primarily in commercial herds owing to expense. Back-yards and small holders are thus at increased risk of FMD, and often serve as virus reservoirs, especially in areas where the risk of FMD incursion is high (Rast et al., 2010). Increased animal populations always create highly susceptible subpopulations and greater risks of FMD exposure and spreading. Quarantine and other biocontainment measures for early FMD cases in affected herds or villages could reduce the spread of disease within and between villages. Increasing overall national herd vaccination coverage, mandatory vaccination, vaccine subsidies, and mass vaccination initiatives should be implemented in endemic countries.

Based in Bangkok, Thailand, the Southeast Asia Foot and Mouth Disease Campaign (SEAFMDC) was launched in 1997 to coordinate subregional control of FMD (Abila and Kalpravidh, 2011). The trans-boundary nature of FMD suggests that efficacious FMD control may depend on the collaborative multicountry disease control initiatives of the SEAFMDC. The FMD laboratory centre in Pakchong, Thailand, has been recognized as an OIE Reference Laboratory for FMD, serving as a hub for diagnostic support and vaccine production in SEA. To identify the risk factors and critical points of animal movement for FMD control, social networks and relevant stakeholders should work together to devise mutually accepted regulatory and non-regulatory recommendations to reduce the risks of FMD spreading in their respective countries. A zoning system is recommended for FMD endemic countries, such as Thailand, that wish to propose an FMD-free zone, such as that currently being established in eastern Thailand. However, establishing FMD-free zones can be problematic, as measures for strict biosecurity control may affect the daily lives of native residents. Sustained commitments from governments, cooperative diplomatic relationships, and public awareness campaigns are critical to FMD control to ensure collaboration among veterinarians, traders and farmers. Encouraging key stakeholders and farmers to follow proper biosecurity measures is critical to effectively limiting disease transmission. The effective eradication of FMD in the Philippines in 2005 and the successful control of FMD in Vietnam in 2006 have been largely attributed to effective strategies for facilitating communication among government officials, veterinarians, traders and farmers (Abila and Kalpravidh, 2011). More intensive epidemiological investigations of outbreaks and continued field research are needed to ensure effective control when future outbreaks occur. Because of its serious direct effect on animal health and production and its indirect socio-economic effect on trade in animals and animal products, FMD is currently a major trans-boundary animal disease in the countries of

mainland SEA. Continued political commitment and proper allocation of resources from each member country are most critical to the success of the SEAFMDC (Abila and Kalpravidh, 2011)

Highly Pathogenic Porcine Reproductive and Respiratory Syndrome (HP-PRRS)

Porcine reproductive and respiratory syndrome virus (PRRSV) was demonstrated serologically in Canada in 1979 and was subsequently isolated in Europe in 1991 (Wensvoort et al., 1991). It has since spread to the rest of the world, where it was serologically demonstrated in Thailand in 1989 (Thanawongnuwech et al., 2004a,b). PRRSV belongs to the family Arteriviridae, genus Arterivirus, generally divided into two major genotypes, European (EU) and North American (NA). PRRS continues to be a major economically important swine disease, especially with regard to co-infection with other respiratory pathogens, as represented in the porcine respiratory disease complex (PRDC) (Thanawongnuwech et al., 2000). Porcine respiratory disease complex symptoms in younger pigs include slow growth, decreased feed efficiency, anorexia, fever, cough and dyspnoea. Reproductive failure in sows and temporary infertility in boars are also prominent in susceptible breeders. Antigenic and genetic heterogeneities of PRRSV and quasispecies evolution are well described (Goldberg et al., 2003; Schommer and Kleiboecker, 2006). Coexistence of mixed PRRSV genotypes or strains within the same herd becomes potentially problematic to control, as cross-protection can vary from complete to non-existent (Thanawongnuwech et al., 2004a,b), and inter-strain recombination has been observed in the field in China (Li et al., 2009), all of which serve as significant obstacles to effective transmission control using vaccines and management strategies.

Recently, North American PRRSV strains with a nucleotide deletion in the nsp2 coding region have been reported in USA, China, Japan, Denmark and Vietnam (Gao et al., 2004; Han et al., 2006; Li et al., 2007; Feng et al., 2008; Yoshii et al., 2008). Following the outbreaks of swine high fever (SHF) syndrome caused by highly pathogenic (HP)-PRRSV in China, many genetic variants of this particular Chinese virus have been subsequently characterized, and recent data suggest that those variants originated from the CH-1a strain isolated in southern China (An et al., 2010). The severe clinical manifestation of this particular Chinese HP-PRRSV could possibly be caused by a combination of HP-PRRSV and other pathogens such as classical swine fever virus (CSFV), porcine circovirus 2 (PCV-2), or non-pathogenic *Streptococcus suis* serotype 7 (Xu et al., 2010). Strains of Chinese HP-PRRSV containing typical two discontinuous sequence

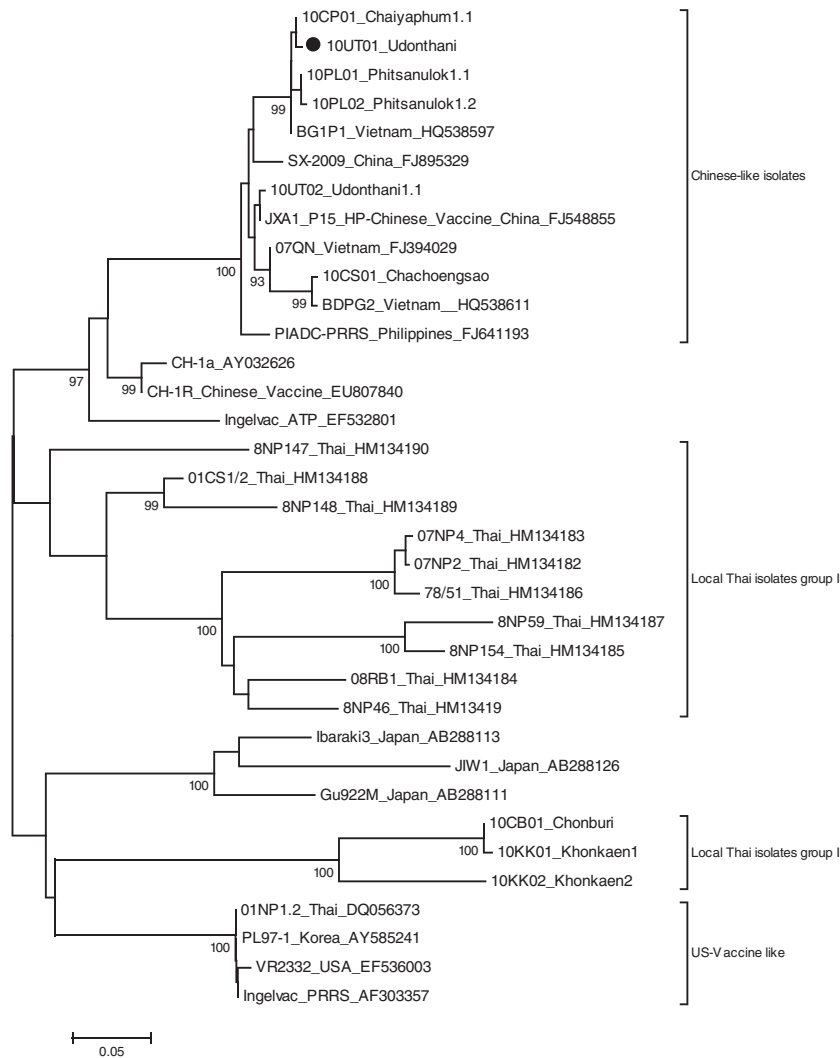


Fig. 1. Phylogenetic analysis based on nucleotide sequence of NSP2 region. Dark dot represents the first Thai HP-PRRSV isolated in 2010.

deletions in the *nsp2* gene were initially identified in 2006 and have continued to cause economic damage in China, Vietnam (Wu et al., 2009), the Philippines, Lao PDR and more recently in Thailand's NongKai province (August 2010), where high mortality rates in all age groups were similar to previous outbreaks in Lao DPR. Concurrently, PCV2 and CSFV were also demonstrated by PCR (Chulalongkorn University-Veterinary Diagnostic Laboratory, CU-VDL) in the affected tissue samples from NongKai province. Trans-boundary transmission of HP-PRRSV likely occurs via the pig trade in the border areas, as epidemiologic evidence suggests for outbreaks that occurred early in northern (April 2010) and southern (July 2010) Vietnam (Tung et al., 2011), Lao DPR (June 2010) (Phommachanh et al., 2011), Cambodia (July 2010) (Theary et al., 2011), Thailand (August 2010) and Myanmar (Febru-

ary 2011) (Ling Ling Bo, 2011, personal communication). Trans-boundary spreading of HP-PRRSV from southern China to SEA clearly represents biosecurity failures through failure to control the animal movement and trading among neighbouring countries at the border areas. Spreading of the virus within a country also confirms the failure of biosecurity control, primarily via uncontrolled human movements within highly contaminated areas, especially at loading zones and slaughter houses (R. Thanawongnuwech, personal observation). Sharing such contaminated areas with other vehicles may increase pathogen spreading within the community.

Multiple introductions of HP-PRRSV into Thailand are also evident based on the phylogenetic analysis (Fig. 1) and the report of Tung et al. (2011), demonstrating that at least two subclusters of the Chinese HP-PRRSV (2007

and 2010) were found in Thailand. In addition, a recent isolate (10UT02_Udonthani1.1) is genetically very similar to the Chinese HP-PRRS MLV vaccine (JXA1; Beijing Anheal Laboratories Co., Ltd., Beijing, China). It should be noted that the Ingelvac® PRRS ATP vaccine (Boehringer Ingelheim Vetmedica, Inc., St Joseph, MO, USA) is also genetically quite similar to the HP-PRRSV. A highly virulent strain, atypical PRRSV, which emerged in the United States in 1996, is the parent strain of the Ingelvac® PRRS ATP vaccine (Kim et al., 2008). Coincidentally, the atypical PRRSV and the Chinese HP-PRRSV did cause similar clinical signs, including the sow abortion and mortality syndrome. These viruses might share some virulent factors genetically. The evolution of the Chinese HP-PRRSV needs further investigation.

Although the deletions in the *nsp2* gene were previously thought to contribute to the virulence of the Chinese HP-PRRSV, *in vivo* experiments have not indicated such (Zhou et al., 2009). It should be noted that PRRSV virulence among strains cannot be differentiated *in vitro*. Indeed, the genetic, antigenic and pathogenic variability among PRRSV strains has drawn great attention for vaccine and diagnostic development.

The HP-PRRSV affects all stages of production. Pregnant sows manifest abortion and give birth to weak and stillborn piglets. Morbidity and mortality rates of 50–100% and 20–90%, respectively, have been observed in nursery piglets, growing pigs and pregnant sows (Zhou et al., 2009). Interestingly, HP-PRRSV was recently reported to induce subverting of the host innate immune response, in which the apoptotic state was inhibited, and the expression of CD163 was upregulated. These effects reportedly contributed to premature interleukin 10 production, potentially prolonged lifespan of macrophages and increased the yields of progeny virions, which were manifested in severe necrosis and increased pathogenicity (Xiao et al., 2010).

Surveillance and monitoring should be routinely conducted in the affected countries. Risk factors for PRRSV infection include variation in biosecurity levels, animal and animal product movement within and between countries, increasing herd size, high pig density, and exposure to PRRSV-infected animals, infected semen, or vaccinated neighbouring herds (Mortensen et al., 2002; Christopher-Hennings et al., 2008). The primary routes of PRRSV transmission include direct contact, aerosol transmission, vertical transmission in sows, infected semen for AI and mechanical infection via infected needles or carrier insects (Pitkin et al., 2009a,b). Therefore, great potential for horizontal transmission exists at virtually all stages of production (Wills et al., 1997). Thus, intervention strategies designed to prevent both vertical and horizontal transmission are key components to PRRSV control.

Management strategies for controlling PRRSV should also include more rigorous biosecurity, sow-herd stabilization by herd closure and closed herd, all in/all out practices, medicated early weaning, segregated early weaning, nursery depopulation, and vaccination. Efforts to educate farmers and the general public in effective measures to prevent transmission and the need for disinfecting equipment are also critical aspects of PRRSV control strategies. In addition, factors that affect animal movements, such as cultural festivities and swine market prices, must also be addressed. While eradication represents the ultimate goal for the HP-PRRSV control, current PRRS control strategies are not predictably successful. Thus, PRRS-associated losses may continue to be seen worldwide, particularly in regard to HP-PRRSV outbreaks in SEA.

Porcine Epidemic Diarrhoea (PED)

Porcine epidemic diarrhoea virus (PEDV), a Coronavirus, is the aetiological agent of porcine epidemic diarrhoea (PED). Porcine epidemic diarrhoea causes acute enteritis and severe diarrhoea with high mortality, particularly in suckling piglets (Pensaert and Yeo, 2006). Porcine epidemic diarrhoea was first identified in England in 1971. It has become a problematic disease, causing economic losses primarily in Europe and Asia (Pensaert and Yeo, 2006; Park et al., 2007; Chen et al., 2008). In late 2007, severe PED outbreaks re-emerged in central Thailand, and the disease is now endemic throughout the country (Puranaveja et al., 2009). Recent PED outbreaks were characterized by severe watery diarrhoea and dehydration with milk curd vomitus in all affected naive suckling piglets. Interestingly, pigs of all ages presented diarrhoea and off-feed to varying degrees, indicating a lack of significant previous immunity. Boars and sows manifested mild diarrhoea and off-feed, but recovered within a few days. When affected suckling piglets were necropsied, the wall of the small intestine was congested, thin and demonstrated segmental enteritis characterized by segmental absence of intestinal lacteal, which likely contributed to malabsorption. Severe atrophic enteritis characterized by blunting of the intestinal villi and sloughing of intestinal epithelium was also prominent in all affected piglets. To control outbreaks in endemic areas, massive feedback of piglet faeces and minced piglet gut to the gestating sows was recommended to prime the immune response and promote lactogenic immunity in suckling piglets. This practice may, however, contribute to the virus becoming endemic in affected farms. Interestingly, immunity from previous endemic PEDV strains and the immunity induced by the commercial Korean vaccine do not provide cross-protection to the recent Chinese PEDV strain

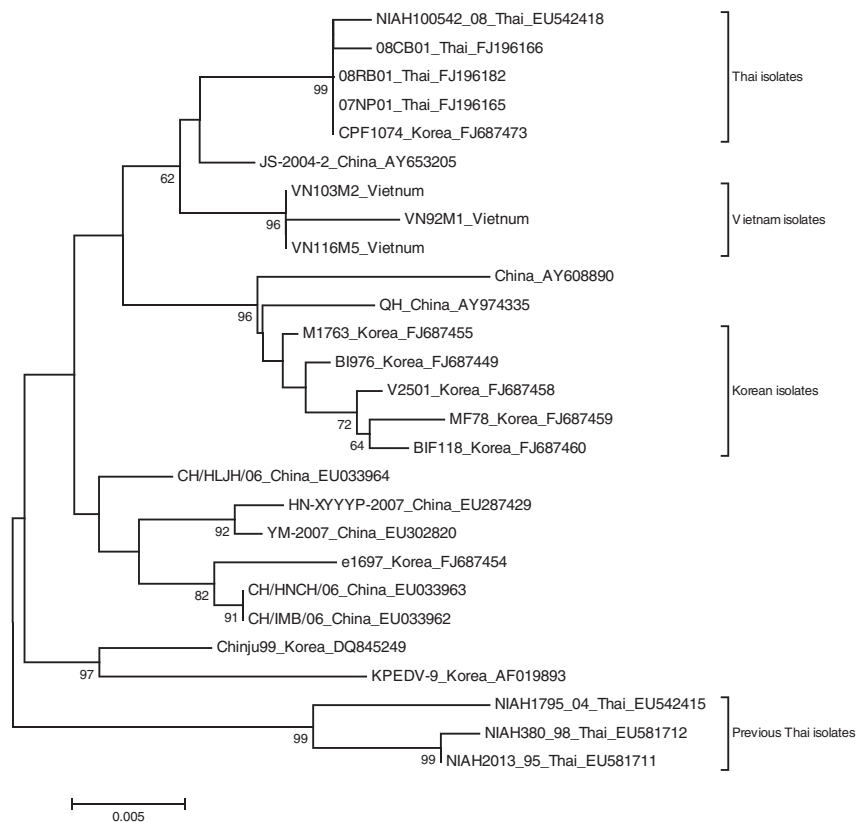


Fig. 2. Phylogenetic analysis based on nucleotide sequence of the M gene of porcine epidemic diarrhoea virus.

(personal observation). As the immunity induced from gut feed back to the sows and replacement gilts is not life long, sporadic outbreaks continually occur in the endemic farms, especially in the subpopulation of non-immunized gilts. If endemic virus is diagnosed in consecutive litters of weaned piglets after an outbreak, virus elimination should be carried out by nursery depopulation or the relocation of infected pigs for 4 weeks post-weaning to avoid re-breaking. The emerging Chinese PEDV is currently prevalent in Thailand and continues to cause sporadic outbreaks. Thus, stimulating PEDV-specific immunity in all stocks is recommended, particularly for replacement animals when facing an acute PED outbreak. Therefore, effective biosecurity control is always a key component of PED prevention and control. Strict sanitary measures should be taken to prevent new introduction of PEDV to the naive farm. Introduction of persistently infected pigs always poses the highest risk, and the disease can also be spread by contaminated vehicles and human traffic between affected farms.

Similarly, emerging PED outbreaks occurred in some southern provinces of Vietnam causing massive economic losses in 2009 (Duy et al., 2011). Acute enteritis occurred in all age groups of pigs. Affected animals, including

suckling piglets, manifested acute watery diarrhoea and dehydration. While most adult animals recovered, most suckling piglets died within a few days. Morbidity in suckling piglets reached 100% in some locations, with mortality ranging from 65% to 91%. Interestingly, the PED clinical symptoms in Vietnam appeared milder than those observed in Thailand, indicating a possible role for virus or pig genetics inducing different pathogenicity.

Phylogenetic analysis of the partial S gene of recent Thai and Vietnamese PEDV isolates indicated that they originated from the same Chinese PEDV ancestor, and these isolates were gradually undergoing genetic variation and forming a new PEDV subcluster in each country (Fig. 2). These data support the observations of other investigators that suggest the Chinese isolate, JS-2004-2, may be the source of outbreaks in neighbouring countries, including Thailand and Vietnam (Puranaveja et al., 2009; Duy et al., 2011). It should be noted that the epidemiology of PED outbreaks in Thailand and Vietnam might not involve the animal movement at the borders, as early outbreaks occurred in the intensive pig raising areas of the countries, rather than the border areas. In addition, recent Korean PEDV field isolates were also genetically similar to the Chinese strains, but differed

genetically from the European strains and vaccine strains used in Korea and China (Chen et al., 2010; Park et al., 2011). Currently, the route of PED introduction into Thailand, Vietnam, and Korea has not clearly been elucidated. Most emerging disease outbreaks are the result of transmission of the causative agent across borders. Interestingly, while reports of PED outbreaks have been widespread in Europe and Asia, none have been reported in the Americas since 1980 (Turgeon et al., 1980). The absence of PED in the Americas is likely attributable to geographic isolation, effective preventive strategies, and biosecurity, as movement of live animals, breeding stocks, and human movement across borders are the major risk factors for the transmission of most emerging trans-boundary diseases.

The spread of PED between farms and within international borders may be caused by several major risk factors, including poor biosecurity and ineffective decontamination of fomites. Following the introduction of PED by such means, animal and human movements contribute further to transmission among neighbouring farms. Establishment of a national strategy for prevention and control of PED requires blocking the epizootic–enzootic circulation of the virus. Therefore, the clear elucidation of origin and transmission routes of this emerging Chinese-like PEDV will contribute to a better understanding of risk factors and the development of effective prevention and control strategies. The presence of the Chinese-like strains in Thailand, Vietnam and Korea raise major questions regarding which currently available PEDV vaccine will be most effective for controlling the Chinese-like PED epidemic.

Conclusion

Similar to the H1N1 pandemic of 2009, increasing globalization has likely contributed to the recent emergence of trans-boundary swine diseases in SEA (Sreta et al., 2010). Disease transmission can occur through the movement of infected animals and animal products, contaminated vehicles, and human traffic, particularly animal workers and traders. Surveillance of the infectious agents must include both wild and domestic animal populations and their environments and should be internationally coordinated through the establishment of a collaborative network. For example, FMD risk assessments should involve collaboration among neighbouring countries. Neighbouring government authorities, veterinarians, social networks, stakeholders and farmers must work together to identify the risk factors to reduce trans-boundary FMD virus transmission. Fortunately, FMD vaccination can be effective when used uniformly to prevent and control the disease. Unlike FMD virus, the current HP-PRRSV control

strategies are not predictably successful, neither conventional control strategies, nor commercially available vaccines, owing to native virulence, a lack of cross-protection, and severe immunosuppressive effects. Rigorous biosecurity must ultimately play a critical role in HP-PRRSV control if eradication is to be achieved. Similarly, the Chinese-like PEDV has become endemic in Thailand and Vietnam, and sporadically causes problems in subpopulations of naive suckling piglets in endemic areas. Current commercial PED vaccines do not induce effective lactogenic immunity to the Chinese-like PEDV. As practicing gut feed back to the sows and replacement gilts may contaminate the herd with unwanted organisms, virus elimination should be carried out by sow-herd stabilization and nursery depopulation to avoid re-breaking with the virus. Sustained maintenance of sow immunity prior to farrowing by whole herd and regular gilt acclimatizations may represent an alternative tool for control of PED. Lastly, the support of the OIE and FAO in designing surveillance and control methods specifically for these Asian countries would highlight the global importance of efforts to stem the spread of these infectious trans-boundary swine diseases.

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Conflict of interest

All authors declare no conflict of interests.

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