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Emerging Zoonoses in Domesticated Livestock of Southeast Asia

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Glossary

Emerging disease New infections resulting from the evolution or change of an existing pathogen or parasite resulting in a change of host range, vector, pathogenicity or strain; or the occurrence of a previously unrecognized infection or disease.
Endemic Prevalent in or peculiar to a particular locality, region, or people.
Evolution Evolution is the process by which genetic mutations that enhance reproduction become and remain more common in successive generations of a population.
Livestock Livestock are domesticated animals raised in an agricultural setting to produce commodities such as food, fiber, and labor.
Mutation A change in the DNA sequence.
Pandemic An epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people.
Reassortment Mixing of the genetic material of a species into new combinations in different individuals.
Recrudescent Breaking out again: renewing disease after abatement, suppression, or cessation.
Risk factor/determinant A variable associated with an increased risk of disease or infection.
Synergism Interaction of discrete agencies conditions such that the total effect is greater than the sum of the individual effects.
Zoonoses Diseases that is transmissible between vertebrates and humans.

Introduction

Southeast Asia (SEA) is known for its physical, political, cultural, and socioeconomical heterogeneity and is geographically divided into mainland and maritime (or Malay Archipelago) SEA comprising of Cambodia, Laos, Myanmar, Thailand, Vietnam, Peninsular Malaysia and East Malaysia, Brunei, Indonesia, the Philippines, Singapore, and East Timor, respectively. In the past two decades several zoonotic diseases, i.e., diseases that are transmissible between humans and animals (vertebrates), have surfaced in SEA, severely affecting the regional economy and devastating animal and human lives. The disease events reserved SEA as among the regions to be monitored for future emerging zoonotic diseases (Gilbert, 2012).

According to the World Organisation for Animals Health (OIE), emerging zoonoses are "new infections resulting from the evolution or change of an existing pathogen or parasite resulting in a change of host range, vector, pathogenicity or strain; or the occurrence of a previously unrecognised infection or disease" (WHO, 2011). While reemerging zoonoses are existing or endemic (possibly hypoendemic) communicable diseases resurging in terms of their frequency (incidence or outbreaks) or distribution over space and time, emerging zoonotic diseases may arise sporadically due to unique combinations or 'synergism' of several disease drivers, such as those that were seen in the explosive outbreaks of Nipah virus infection, SARS (severe acute respiratory syndrome), and the recent influenza H1N1 pandemic of 2009 (Morens and Fauci, 2013). These events usually attract more attention among the public and scientific community as they can be distinctive in terms of presentation and extraordinary in terms of magnitude, coverage, and socioeconomic implications.

Livestock farming is the principal source of livelihood for most countries in SEA except Singapore and Brunei. SEA is home to an estimated more than 2.65 billion chickens, 245 million ducks, 13.7 million head of buffalo, 46.1 million head of cattle, 71 million head of pigs, 13.8 million head of sheep, and 28.2 million head of goats (FAO, 2014). Animal agriculture and related activities in this region provides employment and side income, improves household dietary components and nutritional security, and provides food and economic well-being for their respective nations' (Randolph *et al.*, 2007). In the past decade, some of the livestock sectors in this region such as the poultry sector have significantly expanded. However, the rate of expansion is not even across the region whereby larger scale poultry farming is propagating, i.e., it is rapid in Thailand and Malaysia, but at a much lesser extent in Vietnam, Indonesia, and Cambodia. Nonetheless, livestock rearing in SEA has remained the practice of smallholders where the majority of livestock are reared in an extensive or backyard system (Ahuja, 2013; Del Rosario *et al.*, 2007). This type of animal husbandry has been linked to several emerging diseases and has been identified as a risk factor for future emerging infections (Biswas *et al.*, 2009; Grace *et al.*, 2012).

The poor 'bear a disproportionately high share of the burden of (zoonotic) disease' because of their close contact with livestock in unsanitary conditions and the low likelihood of needed healthcare (Grace *et al.*, 2012; WHO *et al.*, 2006). This is especially true for farmers in Asia and Africa where human and livestock habitat coalesced in small crowded spaces. Livestock agriculture employs more than 50% of households in SEA, among which more than 60% are maintained as backyard farms where biosecurity is almost impossible to implement. The unsophisticated nature of backyard system allows continuous interaction between various species or animals and humans and has been frequently reported as one of the most important emerging disease determinant in this region. In 2012, International Livestock Research Institute, Kenya produced a comprehensive report about transmission of disease in emerging

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livestock systems in the developing world, and in the report the institute mapped poverty to zoonoses occurrence worldwide (Grace *et al.*, 2012). SEA was highlighted as among the areas with high concentration of poor livestock keepers where intervention at the human–livestock interface could give positive impacts on zoonoses control. This article will highlight only the major emerging zoonosis and lingering or endemic zoonosis caused by infectious microorganisms originating from domesticated farm animals that have been reported in the SEA region for the last two decades. Non-zoonotic and transboundary emerging animal diseases of food security and economic importance will not be discussed.

Factors Influencing the Emergence of Zoonotic Infectious Diseases among Livestock in Southeast Asia

A combination of factors has been linked to the emergence and resurfacing of zoonotic and non-zoonotic trans-boundary diseases, which have been discussed extensively elsewhere. Briefly, the factors include microbial evolutionary adaptation such as genetic mutation and viral genetic recombination or reassortment, improvement of microbial switching capacities between host species, change in the size of susceptible or reservoir host populations, changes in human behaviors (particularly dietary choices, movement, and travel) and changes in livestock production and animal husbandry practices including animal trade policy, and ecological/environmental alterations such as for agriculture and urbanization (Brown, 2004; Coker *et al.*, 2011). These microbial, host, and environmental factors interact continuously, therefore actions or activities (intentional, natural, or accidental) that modify any of these key elements might generate opportunities for infectious agents to evolve into new ecological niches, access, and eventually adapt in new host systems.

The SEA region is an emerging market arena because of its changing physical and socioeconomic structures and rapidly expanding populations (Delgado *et al.*, 1999; Pingali, 2007). According to FAO (2012), the total population growth of SEA nations will increase from 523 831 in 2000 to 705 414 by 2030 (FAO, 2013; Jones, 2013). The changing population size and growth estimates have energized the livestock industry to meet the doubling protein demands by 2030 and lend impetus to the 'livestock revolution' in the region (Delgado *et al.*, 1999; Steinfeld, 2004). The growing demand for livestock has encouraged movement of animals and increased the exchange of products, services, and materials between countries. This, in turn, offers new opportunities for smallholder livestock producers in the region to market their products. Unfortunately, regional disharmony in disease control measures, surveillance, and implementation also conveniently allow veterinary pathogens to cross regional borders via legal and illegal animal movement and trade (Coker *et al.*, 2011; Liverani *et al.*, 2013).

SEA boasts a large proportion of the global rainforest and biomes. However, in the past century, an overall 1–2% annual decline of the existing rainforest has been recorded due to various reasons including urbanization, severe weather, logging, intensive agriculture, and industrialized animal production. Intensified farming of major commodity crops such as rubber and palm oil have resulted in clearance of large areas of jungle and forest in Indonesia, Thailand, and Malaysia (Miettinen *et al.*, 2011). The increasing consumer demand for animal product motivate local producers to diversify livestock production system innovatively within these plantations, therefore integrated farming system was widely introduced as it economizes on resources and improves farmer's yield and profits (Devendra, 2011; Devendra *et al.*, 1997). The combinations of crop and animal farming have largely and significantly benefitted the local, national, and regional economy. Nevertheless, the current practice of this farming system in SEA may increase risk of emerging infection via ecosystem–livestock–wildlife interface. According to recent literature reviews, more than 60% from approximately 1400 known pathogens to humans originate from animals, out of which more than 77% are promiscuous and readily infect multiple species including humans (Cleaveland *et al.*, 2001; Kuiken *et al.*, 2005; Woolhouse and Gowtage-Sequeria, 2005). The livestock–crop production within the vicinity of forest situates for livestock–wildlife pathogen exchange. These pathogens may become sustained among wild animals, complicating the control and eradication of livestock diseases. Domesticated animals at the ecosystem–wildlife interface provide a continuous supply of susceptible hosts for the amplification, evolution, and adaptation of novel pathogens from wildlife, serving as important passage for the pathogen to move from wildlife to humans (Chomel *et al.*, 2007; Liverani *et al.*, 2013). Human-origin or anthropogenic disturbances of wildlife ecosystem have in the past led to the emergence of previously unencountered disease agents or organisms blamed for catastrophic disease events such as those seen in the outbreaks of Nipah and SARS (Hughes *et al.*, 2007; Jones *et al.*, 2013).

Impact of Emerging Zoonoses on Southeast Asia

Impact on Food Security

Emerging zoonoses affect food security in two ways; gross reduction at the level of animal production and reduction in numbers of available food animals due to disease or compulsory culling to control the spread of infection to humans. For example, between 2003 and 2013, highly pathogenic avian influenza (HPAI) H5N1 in SEA resulted in the culling of a total of 175 million domestic birds (Van Kerkhove, 2009). In many countries, backyard and small poultry producers were the worst affected. Small- and medium-scale commercial poultry producers had to sell their properties and close their farms when chickens died or were culled whereas backyard producers lost their main source of protein and income (Rushton *et al.*, 2005). At the height of the outbreaks between 2003 and 2005, the production of broilers dropped significantly throughout the region. Thailand, for example, was the fourth largest poultry meat exporter in 2003 exporting nearly 485 000 tonnes of poultry meat. Immediately following the avian flu notification by the Thai authorities in 2004, poultry products were banned from major international trade flows which significantly drove the exportation of poultry down by 50% from 2003, destabilizing the local and regional markets broiler meat supply (Otte, 2008). In Malaysia, reported

clustered outbreaks of H5N1 among a flock of smuggled fighting cocks drove Singapore to restrict chickens and eggs imported from Malaysia as a precautionary measure to the perceived risk. As a result of the sudden reduction of supply of these produce, the price of chicken and eggs increased markedly in the local market (Agri-Food and Veterinary Authority of Singapore, 2004; Nicita, 2008), lowering consumer's purchasing power for basic necessities. Fortunately, the outbreak was rapidly controlled by the veterinary authorities and customer confidence and trade was therefore restored.

The worldwide outbreak of pandemic influenza A H1N1 2009 was initially linked to pigs because the genetic makeup of the virus partly includes swine-originated influenza genes (Malik Peiris *et al.*, 2009). It was apparent in the course of the outbreak that pigs played no active role in the pandemia and the epidemiology of the disease, but because of the partial genetic affiliation, the media-friendly 'swine flu' was used in reference to the disease (WHO, 2009). The term led to serious misunderstanding among consumers about the safety of consuming pork and pork products worldwide. As a consequence, many refrained from purchasing pork, leading to domestic and regional pork markets downturn. In fact, pork-importing countries within the region considered introducing trade restriction on live pigs as precautionary measures to safeguard the local pig industries and preserve human health (Johnson, 2009). At the same time, various groups in the region further insisted on stamping out all pigs to reduce risk of disease, even when neither viral evidence nor infection was observed. Outside of SEA, in Egypt, mass pig slaughtering was performed amidst fear of virus spread (Gusman, 2009). However, prompt risk communication emphasizing the lack of danger posed by pigs or pork restored consumer confidence and minimized the potentially disastrous consequences to the pig production industry in the region.

Impact on Human Health

The overall disease burden to human health is usually expressed as disability-adjusted life year (DALY), which measures the year lost due to ill health, disability, and early death (Lopez *et al.*, 2006). However, the true burden of emerging and reemerging zoonoses is difficult to estimate due to the lack of comprehensive information and systematically collected data worldwide. The OIE reported zoonosis to cause at least 2.4 billion cases of illness and 2.2 million deaths every year (Grace *et al.*, 2012). Reemerging zoonoses, which are often considered neglected, are the hardest to estimate because the prevailing cases occur in underdeveloped or developing nations including SEA, where data are not available or poorly recorded, stored, and managed. Systematic reports of cases – if present – are often not accessible and questionable data integrity makes estimation of disease impact challenging. However, it is universally accepted that zoonosis among livestock have in the past and will continue to cause extensive human sufferings and deaths. Classical zoonosis such as brucellosis, for example, resulted in major disability and debility of military personnel during World War II with more than 1300 cases reported in the US Army between 1942 and 1945 (Wyatt, 2013). Many soldiers contracted brucellosis through consumption of contaminated raw milk and cheese and later had to be discharged because of severe debility as a result of prolonged fever and complications caused by arthritis. The disease has continued to contribute to the global burden of human illnesses and sufferings (Dean *et al.*, 2012; Pappas *et al.*, 2006) especially in developing nations such as Syria and Mongolia. Recent emerging zoonoses such as HPAI H5N1 killed 383 of 647 infected people worldwide since 2003 while avian influenza H7N9 has resulted in 145 infections with 45 deaths (WHO, 2013) since early 2013. Novel Nipah virus infection in Malaysia and Bangladesh caused more than 270 deaths and chronic debilitating post-encephalitic conditions to many others.

Impact on Social and Economy

A recent study estimated the costs of major highly fatal zoonoses between 1997 and 2009 to be US$80 billion (World Bank, 2012). The socioeconomic impact of zoonoses includes the loss incurred from reduced livestock production, trade restrictions, declined consumers demand for products, and disease control/prevention activities including surveillance efforts. In addition, it includes the indirect cost of depressed economic activities of other businesses dependent on the livestock industry such as animal feed manufacturers, animal-related food producers, food retailers, and hospitality services (Otte *et al.*, 2004; Rushton, 2009). Non-affiliated activities such as tourism can also be negatively affected as reported during the outbreak of SARS and pandemic influenza H1N1 2009 (Coker *et al.*, 2011; Lau *et al.*, 2009).

The socioeconomic repercussion of emerging zoonoses was well documented for Nipah disease event in Malaysia (Ng *et al.*, 2009). The outbreak resulted not only in the culling of over one million pigs but also bankrupting town economy when residents moved away from affected areas. Nipah essentially destroyed the local pig industry at the time and the livelihood of many pig farming families. For example, an estimated 36 000 employment opportunities in the farms and other local business that were supported by the farming activities diminished and local town and real estate businesses had to close down when pig farm operations liquidated. The value of destroyed pigs was estimated at US$97 million with additional US$35 million losses for compensation paid by the government and US$120 million in trade to Singapore and Hong Kong (Nor and Ong, 2000). The effect of Nipah rippled or spread to other pig affiliated industry causing indirect losses to pig feed industry, oil and fats, utility, and real estate which amounts to RM 541 million (US$164 million) (Hosono *et al.*, 2006). Following the outbreak, the number of pig farms dropped from 1800 prior to January 1999 to only 796 after 21 July 1999 (Nordin, 2001) with most pig farmers leaving the pig industry for other livestock or unrelated animal farming opportunities.

On a larger scale, the HPAI H5N1 epidemic in the region had a similar impact as the Nipah outbreak in Malaysia. Direct losses to the poultry sector were as the result of massive culling of affected and at-risk flocks with estimated cumulative losses of up to US$10 billion between 2003 and 2005 in SEA alone (FAO, 2005). However, more costs from the disease ensued indirectly. For example, Malaysian exporters reported a combined loss of RM 2 million per day (US$526 000) as a

result of the trade restriction to Singapore, a 20% drop in local consumer demand for chicken, and a consequential reduction in the average chicken price. Additional costs were incurred from concurrent control measured implemented such as movement controls, active and passive surveillance, and public awareness campaigns. Malaysia spent an estimated US$50 000 per month in 2005 on movement control alone (FAO Regional Office for Asia and the Pacific, 2006). During the outbreak, Vietnam and Indonesia had to embark on mass vaccination of poultry as the number of human cases increased and had to invest in cold chain assurance of the vaccine, training of vaccinators, and mass communication campaigns. The total costs of delivering vaccinations alone during the first year of vaccine implementation in these countries were estimated to be US$22 million (Pongcharoensuk *et al.*, 2011).

Emerging Viral Zoonoses in Southeast Asia

Nipah Virus Infection

Between late 1997 and early 1998 a mysterious 'barking pig syndrome' appeared in a pig farm at a northern state of Peninsular Malaysia that rapidly spreads to the central states (Mohd Nor *et al.*, 2000). The disease in pigs was closely linked to clustered cases of febrile encephalitis among individuals occupationally exposed to pigs and led to the discovery of the novel Nipah virus (Chua *et al.*, 2000). In the initial phase of the outbreak, the clinical signs observed in pigs ranged from mild to severe respiratory symptoms with variable neurological signs, but with prevailing low mortality rates. A distinctive dry hacking cough from infected pigs resulted in the coined 'barking' syndrome which could be heard from a distance away. Within an incubation period of 7–14 days of exposure to infected pigs, farmers, and abattoir workers showed neurological clinical symptoms related to meningitis such as hypotonia, areflexia, segmental myoclonus, disorientation and confusion, and convulsion, which rapidly progressed to coma and death (Chua, 2003; Lam and Chua, 2002). The case–fatality rate from those infected was 40%, where 106 deaths occurred among the 265 infected by the end of the outbreak in 1999. Individuals who survived the infection had prolonged or permanent disabilities and approximately 8% of those who survived succumbed to recurrent neurological disease due to viral recrudescence (Chong and Tan, 2003; Tan *et al.*, 2002).

The Nipah virus, named after the location where the disease was first discovered at Sungai Nipah, Negeri Sembilan is antigenically and genomically similar to the Hendra virus isolated from bats in Australia and was later classified into a distinct taxonomic unit as the new genus *Henipavirus* of the family *Paramyxoviridae* (Chua *et al.*, 2000). A retrospective analysis of serum stored at the Veterinary Research Institute in Ipoh, Perak later indicated that the agent may have been circulating in the pig population in Malaysia as early as the mid-1990s. However, the impact among pigs may have been insignificant and humans were not affected allowing the disease to go unnoticed. Pigs were identified as the amplifier host for Nipah virus, resulting in the culling of approximately 1.1 million pigs as part of the outbreak response (Mohd Nor *et al.*, 2000; Nor and Ong, 2000). Most, if not all pig farming in Malaysia is done intensively, therefore culling was performed swiftly and efficiently via local intersectoral and interagency efforts. Backyard pig farming being uncommon in Malaysia combined with the fact that pig farms were located at a certain distance away from the residential areas may have helped curb the magnitude and spread of the outbreak. The culling of pigs was followed closely by diminishing cases of the disease among humans. Nipah outbreak has not been reported since.

Pteropus bats (flying foxes or fruit bats), which were found at the index farm, have since been proven in many studies to be the symptomless reservoir host of the virus (Halpin *et al.*, 2011; Rahman *et al.*, 2010; Yob *et al.*, 2001). The species that have been well studied for Nipah virus infection are *Pteropus vampyrus* (large flying fox) and *Pteropus hypomelanus* (island flying fox) (Chua *et al.*, 2002b; Epstein *et al.*, 2009; Rahman *et al.*, 2010, 2011, 2013; Yob *et al.*, 2001). Pteropid bats have coevolved with the virus over time and are more likely to shed the virus during reproductive seasons or following stressful events (Halpin *et al.*, 2011; Rahman *et al.*, 2011, 2013). Infected bats shed the virus in secretions and excretions such as saliva, urine, semen, and feces (Halpin *et al.*, 2011). Apart from bats in Malaysia, serological evidence of Nipah virus has been found in pteropids trapped throughout SEA such as Cambodia, Indonesia, and Thailand (Reynes *et al.*, 2005; Sendow *et al.*, 2006; Wacharapluesadee *et al.*, 2005), a finding that is not surprising given the distance traveled and migratory nature of these bats (Breed *et al.*, 2010; Epstein *et al.*, 2009). The spill-over event may have occurred when bats which were believed to have migrated from Borneo were attracted to fruit trees planted around pig farms and near pig pens, a practice that was abandoned following the Nipah. Pigs may have consumed partially eaten fruits contaminated with fluids or excreta from the bats. The virus was then amplified in pigs and consequently spilled to in-contact farm workers resulting in the outbreak (Chua *et al.*, 2000; Mohd Nor *et al.*, 2000). Outbreaks have not occurred in other countries that reported serological evidence of Nipah antibodies among sampled bats and no evidence of seroconversion have been reported in humans or domesticated animals in the respective countries.

The emergence of Nipah in Malaysia is unique and has since been linked to the extraordinary convergence of climatological and ecological drivers which created an ideal situation for the virus to surface (Chua *et al.*, 2002a; Epstein *et al.*, 2006; Field *et al.*, 2001). Complex interaction between urbanization, deforestation, and extreme climate changes were believed to have driven the bats from their natural ecosystem to another in search of food. At present, Malaysia has remained free from the Nipah disease and pigs screened in the yearly Nipah serosurveillance have not shown any evidence of Nipah virus antibodies. Nipah outbreaks have continued to occur in Bangladesh, where an obvious amplifier host has not been identified and the human-to-human transmission that was unobserved in the Nipah outbreak in Malaysia was evident (Homaira *et al.*, 2010; Hsu *et al.*, 2004).

Emerging Influenza A Viruses

Influenza viruses are members of the family *Orthomyxoviridae*, a group of single-stranded, negative-sense ribonucleic acid

(RNA) viruses and are classified on the basis of antigenic differences among their nucleopcapsid and matrix proteins as Influenza A, B, and C. Of these three, only influenza A viruses are established in different animal species including humans, horses, swine, and a wide variety of domesticated and wild birds. Influenza A viruses are further divided into subtypes based on the antigenic relationships of their hemagglutinin and neuraminidase surface glycoproteins (Lee and Saif, 2009). These viruses inhibit the gut of wild waterfowl, its natural reservoir, but are highly capable of evolving in aberrant hosts. Influenza A have been successful in developing various mechanisms to jump species – into domestic poultry, farm animals, and humans after undergoing 'genetic shift,' a periodic gene segment reassortment between host species that produce significant antigenic change improving virus capabilities to infect new host species (Chen *et al.*, 2004; Webster *et al.*, 1992).

Highly Pathogenic Avian Influenza A H5N1

The HPAI H5N1 causes severe morbidity and mortality among poultry and was the first avian flu to cause severe respiratory disease and high mortality among humans. In SEA, the reported case-fatality rate of H5N1 infection in humans vary between 50% and 80%, however the rate is acknowledged to be inflated due to an undetermined number of individuals who may have been silently or subclinically infected during the outbreaks (Le *et al.*, 2013; Wang *et al.*, 2012). The incubation period of H5N1 in chickens is tricky to measure but has been estimated to be between 2 and 3 days (Bouma *et al.*, 2009; Jeong *et al.*, 2009) in experimental settings after which highly variable clinical presentation developed that includes respiratory symptoms such as ocular and nasal discharges; coughing; snicking; dyspnea; swelling, of the sinuses and/or head; severe depression; reduced vocalization; marked reduction in feed and water intake; and cyanosis of unfeathered skin, wattles, and comb. Incoordination and nervous signs, diarrhea, drastic decline in egg production, and increased poor-quality eggs and sudden deaths (high mortality of up to 100%) were also reported. In domestic ducks, with an exception of rare sporadic outbreaks most HPAI viruses produce few clinical signs (Chen *et al.*, 2006; Ellis *et al.*, 2004). Viral transmission may occur when infected birds shed the virus via discharges from its body (saliva, respiratory discharges, and feces), or via contaminated fomites (feed, water, etc.) to susceptible hosts. Once exposed to infectious birds, the incubation period for susceptible humans have been reported to range between 3 and 9 days (Huai, 2008) leading to initial symptoms of headache, myalgia, diarrhea, sore throat, and rhinorrhea followed by fever, cough, and shortness of breath. At a later stage of infection, severe lower-respiratory-tract symptoms and deaths were frequently reported. The case-fatalities for H5N1 infection in humans varies between countries within the region depending on several factors such as accessibility to medical care, culture and belief of people, and the socioeconomic standing of the country's general population.

H5N1 virus has emerged as early as 1996 in farmed geese in Guangdong Province of southern China but was not notable until the H5N1 virus made a dead-end jump from poultry to humans in Hong Kong in 1997, where the outbreaks of H5N1 infection in poultry coincided with severe respiratory infection and fatalities in humans (Chan, 2002; Guo *et al.*, 1998). Avian influenza was formally reported in SEA in Vietnam at the end of 2003. The infection rapidly spread in the country's poultry population where severe respiratory infection and lethality occurred among poultry and humans. Within a few ensuing months the disease had spread to Thailand, Cambodia, Indonesia, Laos, and Malaysia (Sims *et al.*, 2005; WHO, 2012). Most outbreaks occurred among backyard poultry with instances of virus transmission to local commercial poultry farms usually via fomites (such as trucks, crates, and cages) and personnel. Even though the poultry industry is the major livestock industry undergoing rapid intensification in this region, 50–70% of poultry are raised in backyard farms where little biosecurity exists (Bethe, 2006; Boni *et al.*, 2013).

The risk factor for infection of H5N1 in human has been well reported. A paper published by Van Kerkhove provides a comprehensive review on the modes of virus transmission (Van Kerkhove, 2009). Consistent with the widely practiced backyard farming system, the most important and consistent risk factor for human infection across studies involves varying level of contact or exposure to live infected poultry. Direct contact when handling sick birds, consuming uncooked poultry products, and caring for sick poultry are some of the significant determinants found in most human avian influenza outbreaks. The environmental risk factor include local animal trade pattern (such as informal trading in the local community and trading live animal in markets), extent of surveillance and early detection, density of live animal markets, poultry husbandry system, density of free ranging chicken and ducks, and rice cropping intensity. Live poultry market is one of the most discussed determinant for avian flu (and a few other emerging zoonoses). This type of market supplies 'warm' meat preferred by most Southeast Asian countries and is widely found in this region. However, the activities and environment of the market apparently promote virus from infected birds to circulate and spread to other birds and humans via aerosolized virus particles, blood, or body fluids (Fournié *et al.*, 2012; Van Kerkhove, 2009). A few countries in SEA have since discouraged operations of live poultry markets to reduce the risk of emerging diseases. However, little success has been achieved in this effort because of cultural affiliations of this practice to the people in this region. Changes can only be seen with public education and awareness, and implementation of regulations by the local authorities.

Since its emergence in 2003 to January 2014, the World Health Organization has tallied 650 human confirmed cases of avian influenza and 386 deaths worldwide (WHO, 2014). SEA contributed to more than 50% of the cases and fatalities related to human H5N1 infection. Based on the formal notification to OIE between 2003 and 2013, Vietnam surpassed other nations in the world with 2682 outbreaks followed by Thailand with 1141 outbreaks. Indonesia, Myanmar, Cambodia, Laos, and Malaysia each reported 269, 114, 37, 19, and 16 outbreaks, respectively. Malaysia and Thailand have not reported any outbreaks since 2006 and 2009 respectively. HPAI H5N1 outbreaks were better controlled in a few SEA regions compared to others. The success in eradicating H5N1

Table 1 The human cases and deaths due to highly pathogenic avian influenza H5N1 from 2003 to 2013

Country	*2003–09*		*2010*		*2011*		*2012*		*2013*		*Total*	
	Cases	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*
Cambodia	9	7	1	1	8	8	3	3	17	10	38	29
Indonesia	162	134	9	7	12	10	9	9	1	1	193	161
Laos	2	2	–	–	–	–	–	–	–	–	2	2
Myanmar	1	0	–	–	–	–	–	–	–	–	1	0
Thailand	25	17	–	–	–	–	–	–	–	–	27	17
Vietnam	112	57	7	2	0	0	4	2	2	1	125	62
Total	311	217	17	10	20	18	16	14	20	12	384	271

Source: Reproduced from WHO, 2013. Tuberculosis control in South-East Asia Region. Annual TB Report 2013.

virus depends primarily on early detection of virus introduction and prompt institution of control measures such as aggressive culling or stamping-out policy in the country (Coker *et al.*, 2011; Eagles *et al.*, 2009; OIE and FAO, 2007).

Indonesia and Vietnam were the worst countries affected by H5N1 in terms of human incidence and fatalities, which by the end of 2004 and 2005, respectively instigated the decision to perform mass vaccination of poultry (OIE and FAO, 2007). The vaccination was performed along with other control measures such as systematic annual testing and pre-movement testing of local poultry. Both countries have since been considered endemic for avian influenza H5N1. By 2006 Indonesia reported H5N1 outbreaks in 31 of its 33 provinces and 286 of 444 its districts (Sumiarto and Arifin, 2008). Even as this article was being written, Vietnam, Indonesia, Cambodia, Laos, Myanmar, and Indonesia continue to face intermittent outbreaks despite significant control efforts by the governing authorities. However, the incidence and the number of outbreaks in poultry along with those in humans has continuously declined over the past few years consistent with the declining global trend of avian influenza H5N1 worldwide (**Table 1**).

Pandemic Influenza A (H1N1) 2009 Virus

Between March and early April 2009, a novel influenza A (H1N1) virus emerged in the United States among individuals with travel history to Mexico (Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team *et al.*, 2009; Malik Peiris *et al.*, 2009). Initial cases of influenza were later discovered to have occurred in Mexico before it was reported in the United States (Neumann *et al.*, 2009). The virus rapidly spread to the whole northern hemisphere and within the first few months had spread throughout the globe via human-to-human transmission leading to the first global influenza pandemic of the century. The virus was discovered to be the result of novel assortments of triple reassortant avian/human/swine (that include genes from classical swine influenza H1N1, North America avian H1N1, and human H3N2) and Eurasian avian-like swine viruses (Neumann *et al.*, 2009). Phylogenetic analyses suggest that both triple reassorted and Eurasian avian-like swine viruses have become established in the swine population in the late 1990s before the discovery of the novel H1N1. However throughout the outbreak period, no evidence of novel H1N1 infection occurred in pigs other than the possible human to pigs virus transmission on a pig farm in Canada (Howden *et al.*, 2009). It was concluded that even though components of the virus originated from pigs in the past, pigs did not play immediate nor active role in the transmission and epidemiology of the virus in the 2009 pandemia (Johnson, 2009).

The pandemic H1N1 struck almost every SEA countries, and post-pandemic surveillance among pigs in Thailand, Cambodia, and Vietnam suggest that reverse transmission of pandemic H1N1 2009 virus infection had occurred at rates of more than 20% among sampled pigs (Hiromoto *et al.*, 2012; Rith *et al.*, 2013; Sreta *et al.*, 2010; Trevennec *et al.*, 2012). Several phylogenetic analysis work indicated that human-to-swine pandemic H1N1 influenza virus transmission event is not uncommon, a finding that has also been observed for other human seasonal flu viruses (non-pandemic H1 and H3 influenza viruses) therefore implicating human as a significant contributor to the genetic diversity of influenza viruses in swine (Lycett *et al.*, 2012; Nelson *et al.*, 2011). Several episodes of reverse transmission of the virus from infected humans to pigs later proved that pigs will demonstrate very mild flu like symptoms on infection before recovery and can sustain the virus within the flock (Howden *et al.*, 2009; Pereda *et al.*, 2010; Rith *et al.*, 2013; Song *et al.*, 2010; Sreta *et al.*, 2010). At present, there was little evidence to suggest that the virus can be transmitted from infected pigs back to human. However, the finding indicated that countries must improve biosecurity measures at the human–swine interface as pigs are highly efficient in viral recombination and reassortment and thus may impact the human health somewhere in the future.

Low Pathogenic Avian Influenza H7N9

At the beginning of 2013, another avian influenza virus strain of low pathogenicity, H7N9 resulted in severe respiratory infection among humans. The infection first appeared in the southern part of China and later spread to a wider region within the country (CDC, 2013; Gao *et al.*, 2013). The infection in humans are severe and resulted in high case–fatality, however there was little clinical implications to poultry even though epidemiological evidence among human cases highly suggest some level of contact (direct or indirect) with this species (Chen *et al.*, 2013; Lee *et al.*, 2013). Fortunately, the low pathogenic avian influenza (LPAI) H7N9 have to date not been reported among the poultry populations of the SEA countries or any other countries. Many SEA countries imposed

temporary restriction of poultry importation from China to safeguard its substantial poultry farming industry and preserve human health (Lim, 2013; Tuổi Trẻ News, 2014).

Reemerging Endemic Bacterial Zoonoses

Bovine Tuberculosis

Bovine tuberculosis is a classical zoonotic debilitating disease mainly caused by Gram-positive acid-fast bacilli *Mycobacterium bovis* and to a lesser extent *Mycobacterium caprae*. These two species are members of the *Mycobacterium tuberculosis* complex group within the genus *Mycobacterium*. Other species included in this group are *M. tuberculosis*, *Mycobacterium africanum*, *Mycobacterium microti*, *Mycobacterium canettii*, *Mycobacterium pinnipedii*, and *Mycobacterium mungi* (Acha and Szyfres, 2001). Bovine tuberculosis may occur not only in cattle but a wide species of domesticated and wild animals. Bovine species (both domesticated and wild) other than cattle such as buffaloes and bison, and Cervidae such as deer and elk are especially susceptible; however, all warm-blooded species can be infected. Transmission of pathogen between animals occurs via aerosols, ingestion of the organism from contaminated materials, or inoculation via open wound. The incubation period for the disease is highly variable ranging from months to years. The animal may remain asymptomatic for a long period of time following infection, with some proportion of animals remaining latently infected lifelong. Granulomatous lesions or tubercle formations either generalized or localized is a major characteristic of tuberculosis. Infected animals will shed *M. bovis* in respiratory secretions, feces, and milk, and sometimes in the urine, vaginal secretions, or semen. The most usual form of tuberculosis is manifested via a low-grade fluctuating fever, weakness, inappetence, and chronic weight loss leading to progressive emaciation; however, acute and fulminating infection has also been reported (Cosivi *et al.*, 1998). Coughing is not pronounced in animals until lesions occur in the lungs. The chronic development of disease manifestations accompanied by lack of high or immediate mortality often masks the importance of tuberculosis; therefore it is widely believed that prevalence of bovine tuberculosis is under-reported worldwide.

Bovine tuberculosis also referred as 'zoonotic tuberculosis' is a disease of animal production and public health importance. It causes significant economic losses in countries with large cattle farming industry through loss of production, markets and trade, and additional expenditures from surveillance and control programs (Amanfu, 2006; Butler, 2010). SEA with estimated cattle and buffalo populations of more than 110 million (FAO, 2014) will be threatened if the disease is not well controlled. Even though data on bovine tuberculosis prevalence is not available in this region, it can be speculated that the production loss from the disease among cattle will be consistent to what has been observed in developed countries where data are systematically gathered. Accordingly, milk production of infected cattle was reported to decline up to 10% and infected cows had one fewer calves (Cosivi *et al.*, 1998). In countries where food safety regulations are implemented, meat inspection at the abattoir detect clinical signs of tuberculosis such as progressive emaciation and tubercle lesions in the organs, prompting immediate carcass condemnations (Biffa *et al.*, 2010). The impacts of bovine tuberculosis on public health increased where disease is highly endemic and especially affect populations with weakened immune system such those living with HIV/AIDS (human immunodeficiency virus infection/acquired immunodeficiency syndrome) (Cosivi *et al.*, 1998). Conservative estimates reported SEA having more than 3.5 million with HIV (SEARO, 2014), therefore at higher risk for infection compared to the general populations.

For centuries, zoonotic tuberculosis has contributed to the incidence of tuberculosis among humans worldwide. Similar to pathogen transmission between animals, zoonotic transmission of *M. bovis* from animals to human occurs primarily through consumption of contaminated animal products, most commonly unpasteurized milk but may also occur through other mentioned modes (Acha and Szyfres, 2001). However, incidence of zoonotic tuberculosis markedly declined following the introduction of pasteurization and structured veterinary disease control programs (Cousins, 2001). In general, zoonotic tuberculosis is reported to be responsible for approximately 3–15% of tuberculosis among humans worldwide (Michel *et al.*, 2010; Müller *et al.*, 2013). The rate varies with regions of the world depending on several factors such as veterinary disease control program and food safety regulation in the country. Cosivi *et al.* (1998) estimated zoonotic tuberculosis to be responsible for at least 15 000 DALYs per year (27 DALYs per 100 000 population) in SEA based on the conservative estimate of worldwide proportion of tuberculosis caused by *M. bovis* at 3.1% (Cosivi *et al.*, 1998). Estimation of *M. bovis* contribution to human tuberculosis in SEA is difficult because most laboratories in the region have insufficient capacity to isolate and culture the organism and differentiate *M. bovis* from *M. tuberculosis*, the predominant causal agent for human tuberculosis.

As with many other neglected or lingering infection in developed countries, information about bovine tuberculosis in countries within SEA is scarce or difficult to find. Many disease review efforts suggested little or no data from SEA countries can be accessed via mainstream scientific publications by which burden of the disease can be extrapolated. Evidence obtained from literatures for this article, although few, suggest that tuberculosis is increasingly observed among livestock (and reservoir) in this region, however the prevalence is highly variable. For example, evidence of bovine tuberculosis were found among buffaloes in Thailand at a high rate (Chanepaiboon *et al.*, 2000) and spatial analysis among dairy herds conducted in Thailand suggests herd-level prevalence of 10% and within herd prevalence of between 10% and 30% (Inchaisri *et al.*, 2003). However, limited study on bovine tuberculosis in the neighboring Laos suggested low prevalence at 1% (Vongxay *et al.*, 2012). No other data can be obtained from other parts of SEA even though efforts of controlling bovine tuberculosis are being actively conducted by many SEA countries veterinary services through test-and-slaughter policy combined with abattoir surveillance (FAO, 2012). Formal reports for diseases such as bovine tuberculosis are difficult to obtain due to multiple reasons including poor resource gathering and analytical supports, and lack of priority or emphasis

by respective countries' service institutions for publication of printed materials.

There are several important risks factors for the emergence of tuberculosis among cattle in SEA. The consistent determinants as reported for most underdeveloped or developing nations are lack of structured disease control programs at the farm level and inadequate disease surveillance by local veterinary authorities (Michel *et al.*, 2010; Müller *et al.*, 2013). Testing and culling system is highly resource intensive, therefore might not be performed adequately in many SEA resource-poor areas. Extensive livestock husbandry practices predominantly integrated or mixed farming practices provide additional challenges to disease control because animals may not be easily accessed for disease testing and monitoring. In addition, integrated farms in SEA are mostly located in the peri-urban areas where livestock dwellings coalescence or encroaches wildlife habitats, thereby improving disease spread at the livestock–wildlife and vice versa interface (Daszak *et al.*, 2012; Jones *et al.*, 2013). Wild animals are important reservoirs for *M. bovis* and many sophisticated disease-control strategies in developed nations failed to eradicate *M. bovis* because the organism perpetuates in sylvatic cycle (De Lisle *et al.*, 2001; Gortazar *et al.*, 2011; Nugent, 2011; Schmitt *et al.*, 2002). Wildlife reservoirs may continue to infect susceptible cattle despite avid testing and culling strategies of infected herds. SEA has abundant wildlife and endangered species that can be severely affected if bovine tuberculosis is not controlled. Evidence of tuberculosis infection in wild animals are been seen in a few SEA countries such as Malaysia and Thailand (Angkawanish *et al.*, 2010; Ong *et al.*, 2013). Moreover, wild boars and cervids that frequently roamed in integrated farm areas are well described as maintenance host of *M. bovis* for other domestic and wild animals in many parts of Europe and New Zealand (Jackson, 2002; Meng *et al.*, 2009; Vicente *et al.*, 2006). Tuberculosis among wildlife provides a unique challenge because sylvatic tuberculosis cannot be eradicated through animal testing and culling of precious or protected wildlife species. Any disease interventions will involve complex decisions from various sectors and authorities including the veterinary, wildlife and conservation authorities; biologists; wildlife and ecologists; environmentalists; and the general public (De Lisle *et al.*, 2001).

The WHO (World Health Organization) has recently declared a state of emergency for tuberculosis worldwide. Cambodia, Indonesia, Thailand, and Vietnam reported among the highest incidence of tuberculosis in the region between 2009 and 2013 (WHO, 2013). Tuberculosis in humans is predominantly caused by *M. tuberculosis* which can reversely be transmitted to cattle and a number of other animal species through close contact with infected farm workers or individuals (Ameni *et al.*, 2013; Krajewska *et al.*, 2012; Ocepek *et al.*, 2005). However, the significance of animals as reservoir for *M. tuberculosis* and perpetuator of the infection has not been well documented. Emerging markets in this region demand large human capital investment and services. Therefore, workers from countries ranked with high burden of tuberculosis must be screened before starting work in livestock farms as they can potentially transmit the infection to animals.

Brucellosis

Brucellosis, a disease with many names (Malta fever, undulant fever, Gibraltar fever, etc.) is another classical zoonoses that has lingered for decades and is showing signs of reemergence among animals and humans in this region. Brucellosis is listed as among the most widespread zoonosis worldwide but is often neglected in developing countries. The disease is caused by Gram-negative acid-fast stained bacilli of the genus *Brucella*. Several species of *Brucella* affect animals, however the most important disease-causing species for livestocks are *Brucella abortus*, *Brucella melitensis*, and *Brucella suis*, responsible for bovine, caprine or ovine, and pig brucellosis respectively. Species of *Brucella* are mainly host-restricted however *B. melitensis* has the capacity to infect across the mammalian species and is especially known for its virulence as compared to other species (Acha *et al.*, 2001; Pappas *et al.*, 2006; Seleem *et al.*, 2010).

Brucellosis causes major livestock production losses and is a significant threat to public health. In female animals, brucellosis typically causes abortion at the last stage of gestation. In farms where animal breeding is structured, for example, through synchronous breeding methods, multiple abortions or 'abortion storm' occur acutely in a herd or flock when the organism was first introduced. Infected animals shed *Brucella* via milk and may have subsequent normal parturitions where the organism will be shed through uterine discharges (Renukaradhya *et al.*, 2002). Shedding of the organisms may be lifelong with high proportion of infected animals becoming chronic *Brucella* carriers. In countries of SEA where majority of herd sizes are small and backyard or extensive system predominates, explosive abortions is not typical but seropositive farms will report higher rates of abortion and stillbirths. Lower milk yields of up to 25% have been recorded among infected herds (Acha *et al.*, 2001). In males, organisms are shed via semen and brucellosis may cause orchitis and infertility. The mortality rate is very low ($<2\%$) but extensive morbidity is common within a herd. Brucellosis among humans appear to be directly correlated with the prevalence of brucellosis among livestock as humans contract the infection mainly via consumption of unpasteurized milk or milk products, but may also be infected from eating infected meat, or direct contact with aborted materials from diseased animals. Human to human transmission is rare, therefore control of incidence in humans is best achieved via systematic control of brucellosis among animals. Once exposed to the organism, the incubation period for brucellosis in susceptible animals and humans is variable but ranged from 2 to 4 weeks. The initial sign for human brucellosis includes nonspecific flu-like symptoms of undifferentiated prolonged (undulant) fever, myalgia, and arthralgia with generalized inflammation of the reproductive organs. Clinical manifestations among males include orchitis and epididymitis.

Recent overview of global brucellosis burden indicated absence of data and studies on human brucellosis in SEA (Dean *et al.*, 2012). On the contrary, published data on brucellosis in animals are available but limitations include accessibility and language. Sufficient scientific and local publications exist to indicate that infection is endemic among livestock and is widely spread within respective countries.

Sporadic reports of cases and outbreaks in humans occurred in Thailand, Malaysia, and Indonesia due to various degrees of exposure to infected animals and animal products (Bamaiyi *et al.*, 2011; Danusantoso *et al.*, 1972; Jama'ayah *et al.*, 2011; Paitoonpong *et al.*, 2006; Wongphruksasoong *et al.*, 2012). The reemergence of brucellosis was reported in Thailand in 2003 where *B. melitensis*, a species that has not been reported in Thailand, was first isolated (Manosuthi *et al.*, 2004). Serological surveillance for *B. abortus* in Thailand estimated the prevalence rate of 3.3% in dairy cows (Jittapalapong *et al.*, 2008) with high herd level of 24.1%. In 2009, a large human brucellosis outbreak which caused three deaths was linked to goat herding in a local Thai village (Wongphruksasoong *et al.*, 2012). In certain provinces the seroprevalence among beef cattle reached up to 40% and among sheep and goats, the prevalence ranged from 10% to 20%. In Vietnam, reports of brucellosis in livestock are absent, nonetheless a study on the undifferentiated fever among patients in Vietnam reported 15.8% *Brucella* serologically positive patients (Nga *et al.*, 2006) suggesting that *Brucella* is indeed present among animal populations of Vietnam. In Indonesia, the seroprevalence of *B. abortus* differs widely, ranging between 0% and 46% with high prevalence rate in most provinces of Pulau Jawa and Nusa Tenggara (Putra, 2006). In South Sulawesi, the seroprevalence of brucellosis among Bali beef cattle is high at 19.3% (Mu¯i-hanah *et al.*, 2013). In other parts of Indonesia, the cattle- and herd-level seroprevalence has been reported to be as high as 15–44.5% (Lake *et al.*, 2010), respectively, while the seroprevalence among pigs was 12.6% (van der Giessen and Priadi, 1988). In Malaysia, brucellosis among cattle and goats has lingered for many decades at a low prevalence rate but incidence progressively surged in the early 2000–10 following massive importation of live cattle and goats from *Brucella*-endemic countries late in 1990s. In 2010, several clustered outbreaks of *B. melitensis* among humans were linked to the increasingly popular practice of consuming raw goat's milk (The Star, 2010). Nationwide serosurveilance data suggest that serological evidence for bovine brucellosis of less than 3% is low at animal level but relatively high (21.7%) at herd or flock level (Anka *et al.*, 2013). The direct loss due to brucellosis to the farmers and government estimated from *B. abortus* infection from production losses, carcass condemnation, culling, compensation, and vaccination was approximately RM38 million (US$11 million) for 2010 (Anka, 2014). *Brucella melitensis* have a lower seroprevalence of 0.9% and 7% at caprine level and flock level in Malaysia (Bamaiyi *et al.*, 2010). In the Philippines, porcine brucellosis was a problem in the late 1950s; however, new information is not available to ascertain the current status (San Agustin and Castillo, 1950).

The risk factor of brucellosis in SEA among livestock has not been well studied. However limited studies published in Malaysia and Indonesia suggest that epidemiology of the disease in this region is similar to those in other developing countries (Al-Majali *et al.*, 2009; Muma *et al.*, 2007). Studies on herd-level risk factors for seroreaction to *Brucella* among cattle in Malaysia and Indonesia show extensive farming system to elevate the risk for bovine brucellosis (Anka *et al.*, 2013; Lake *et al.*, 2010). The frequency of wildlife encounter in this farm system is common and therefore was speculated to significantly contribute to the prevalence. As with bovine tuberculosis, wildlife are important reservoir and maintenance host of *Brucella* organism allowing for re-introduction of new infection into clean herds at the wildlife–livestock interface (Bengis *et al.*, 2004; Godfroid, 2002; Meng *et al.*, 2009).

Disease control and eradication program for brucellosis is carried out by most veterinary authorities in SEA countries at different capacities, implementation level, and range of available resources. In some countries such as Indonesia and Malaysia, eradication activities are accompanied by vaccination programs of infected herds to maintain low level of brucellosis at farm level. However, the implementation of vaccination program is mostly irregular, therefore benefits from the vaccination for brucellosis may be hard to assess. In countries where culling accompanied by compensation scheme is carried out, the amount of compensation disbursed generally need improvement as farmers often wavered from culling seroreactors when their losses are not adequately compensated.

Leptospirosis

SEA is endemic for leptospirosis as evident from the continuous reports of human leptospirosis cases and outbreaks. In the last decade, many countries within this region are seeing an increasing number of leptospirosis among humans and the disease has become one of the most important reemerging zoonosis (Pappas *et al.*, 2008; Victoriano *et al.*, 2009). Leptospirosis causes wide range of nonspecific symptoms that may be confused with flu, malaria, dengue hemorrhagic fever, hepatitis, scrub typhus, and many other febrile infections and may be accompanied by acute renal injury or acute lung injury, with case fatalities of 12–25% (Hartskeerl *et al.*, 2011; WHO, 2010). Thus, in countries where these diseases are endemic, leptospirosis is often underdiagnosed, and therefore underestimated. Thailand, Vietnam, Indonesia, and Malaysia have listed leptospirosis as one of the notifiable infectious disease in humans and a disease of priority to control at the respective country's national level.

Leptospirosis is caused the pathogenic spirochete from the genus *Leptospira* which consists of 17 species and more than 250 serovars that are categorized as pathogenic, intermediate, and nonpathogenic leptospirae. The taxonomy of leptopira is highly complex and can be confusing. The article by Bharti *et al.* (2003) provides excellent review on the classification of leptopira and will not be repeated here. Several species are reported more than others in causing clinical infection in both animals and humans which includes *Leptospira interrogans, Leptospira alexanderi, Leptospira fainei, Leptospira inadai, Leptospira kirscheri, Leptospira meyeri, Leptospira borgpetersenii, Leptospira weilii, Leptospira noguchii*, and *Leptospira santarosai*. *Leptospira* serovars may be clustered within geographical region and within a given region only 10–20 serovars are typically found. A number of serovars are found unique and clustered within limited region, however most serovars can be found across geographical boundaries (Nalam *et al.*, 2010). Most mammalian species including domesticated livestock and wildlife are reservoirs of pathogenic leptospires. Some serovars of leptospirae appear to prefer a single host species, however

little information exist about host preference of leptospirae to warrant claims of host specificity (Bharti *et al.*, 2003). Rodents, particularly, have probably coevolved with the spirochete, therefore are highly efficient as the reservoir. The high mobility of rodents further increased their effectiveness as reservoir host and perpetuator of the agent. Other mammals may also serve as important source of the leptospira. Infected mammal may excrete the leptospirae intermittently for months or lifetime thereby increasing the risk for those occupationally exposed to animals such as farmers, slaughterhouse workers, pet traders, veterinarians, rodent catchers, and sewer workers (McBride *et al.*, 2005; Vinetz, 2001).

In SEA, agricultural workers such as paddy or rice farmers are at higher risk of infection compared to individuals of other occupations (Padre *et al.*, 1988; Rafizah *et al.*, 2013; Seng *et al.*, 2007; Tangkanakul *et al.*, 2000, 2005); however, most clinical cases in humans are as a result of environmental contaminations following climatological events such as flooding (Amilasan *et al.*, 2012; Ivanova *et al.*, 2012; Kawaguchi *et al.*, 2008; Lau *et al.*, 2010) or recreational activities (Mortimer, 2005; Sapian *et al.*, 2012; Sejvar *et al.*, 2003). For agricultural workers, the risk is possibly associated with frequent contact with water bodies where livestock are used to assist in plowing the fields and pests such as rats comingle and secrete leptospires. The exact animal species secreting the pathogenic Leptospirae is often difficult to determine as pathogenic serovars often occur in multiple species. SEA has a favorable weather for the survival of leptospira as pathogenic leptospires prefer warm and humid climate (Levett, 2001; Victoriano *et al.*, 2009).

Most literatures from the region suggest that livestock is potentially an important reservoir for pathogenic leptospirae however prevailing evidence indicated that livestock may not be an important source of human infection in the SEA region (Chanepaiboon *et al.*, 2000; Kawaguchi *et al.*, 2008; Van *et al.*, 1998; Victoriano *et al.*, 2009). Clinical leptospirosis in cattle or pigs is rarely reported in any of the SEA countries therefore their clinical, production, public health, and economic implication are unclear. Much of the publications on livestock and leptospirosis in SEA focused on serological surveillance and serovar identification, not their actual role in clinical or human infection. According to literatures, within 10–14 days following exposure, clinical signs of cattle and swine leptospirosis include fever, abortion, still birth, infertility, and milk reduction (Arundel and Radostits, 2000). However, little information could be found on the clinical leptospirosis in livestock in this region, therefore the associated economic or production impact due to leptospirosis is unclear. A study in Vietnam suggest that infection with some leptospira serovars may reduce one live pig born per litter, equivalent to 8% loss of production (Boqvist *et al.*, 2002), no other studies can be found in Asia. In Laos, the serological surveillance using microscopic agglutination test (MAT) suggested that in cattle the leptospirosis prevalence is 53.6% and in pigs 22.7%, however the clinical impact of the prevalence was not evident. Moreover rice field farmers in Laos have significantly higher exposure to the organism whereby 88.7% were leptospira seropositive as compared to 9.3% in livestock farmer (Kawaguchi *et al.*, 2008; Vongxay *et al.*, 2012). In Malaysia, the work on livestock was performed in mid-1980s by Bahaman *et al.* who reported seroprevalence of leptospira species among domestic livestock in Malaysia to average of more than 20%, with highest seroprevalence observed among cattle (40.5%), buffaloes (31%), and pigs (16%) (Bahaman and Ibrahim, 1988, 1986; Bahaman *et al.*, 1987). However, cases of leptospirosis among livestock have never been reported leading many to suggest that leptospirosis is not an important disease of livestock in Malaysia. Furthermore, incidence of leptospirosis in humans in Malaysia is usually associated with recreational and urban exposures rather than agricultural farming activities. Similar observations were recorded in many countries within SEA. Study in Thailand noted little difference in the prevalence of leptopspira antibodies of various livestock between areas where leptospirosis was highly endemic and not endemic among humans. The prevalence of antibodies found using MAT in epidemic provinces was 77.2% in cattle, 86.1% in buffalo, and 60.4% in swine and similar prevalence was observed in nonepidemic province (69.8% in cattle, 82.2% in buffalo, and 62.5% in swine) (Suwancharoen *et al.*, 2000). In general, available evidence at present suggest that livestock is largely exposed to leptospirae organism but manifested little observable clinical signs. Therefore leptospirae may not be a significant agent for disease and production losses among livestock in this region. Livestock might be as important reservoir of leptospira, however their role in the epidemiology of leptospirosis in humans in this region is vague and need to be enlightened with additional studies.

Conclusion

SEA is an arena of emerging markets with human population that is expected to double by 2030. Livestock industries need to significantly expand to ensure adequate protein supply for the growing and more affluent human populations. To increase animal production, various measures were undertaken including expanding agricultural areas and increasing diversity of livestock production systems. Unfortunately these acts are often not supported by increasing environmental and public health regulations in this region. Increased animal movement across borders through legal and illegal trade will continue to occur as long as there is surplus demand for animal proteins. Without harmonization of regional disease controls and strengthening of veterinary disease control programs, emerging disease especially those that had been neglected will continue to threaten regional livestock industry. Deforestation and fragmentation of ecological niches in an effort to expand agriculture land have significantly benefited the local and regional economy and improved society's wealth. However, without doubt these activities are associated with emerging and reemerging infection of production animals in this region. Many infectious diseases in humans originated from animals and agricultural expansion and intensification/diversification promotes disease emergence through ecosystem–livestock–human interface. In addition, encroachments of livestock into wild animal habitat enhance disease transmission at livestock–wildlife interface. The spread of these infections would threaten regional food security and safety. Emerging zoonoses causes major losses through reduced economic activity directly from trade restriction that is often prompted by a nation's

precautionary behavior. The ripple effect from reduction in economic activity can spread to other livestock-related sectors at the national and international levels. Emerging and reemerging infection causes additional cost to the country through general precautionary and preventive measures such as establishment of quarantine station and procedures, restriction of animal importation, premovement testing, vaccination, surveillance, and monitoring. Tremendous downturn in livestock-affiliated economic activity and shock to livelihoods of those affected by the disease warrant collaborative interministrial and intersectoral efforts at national and international level to minimize emerging diseases in livestock and humans.

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