

**WILDLIFE AND HUMAN IMPLICATIONS OF EMERGING
VIRAL ZONOTIC DISEASES IN SOUTHEAST ASIA***Joseph P. Dudley¹***ABSTRACT**

The 7000+ year history of intimate association between humans, wildlife, domesticated livestock and poultry in southeastern Asia makes this area a fertile ground for the evolution and emergence of novel viruses of humans and domesticated animals, particularly viruses that may infect poultry, swine, and/or humans. Recent experiences with the emergence of the SARS virus in Guangzhou and Hong Kong, and the proliferation of a new and more dangerous zoonotic strain of the H5N1 avian influenza virus demonstrate the importance of southern China and nearby areas of Southeast Asia as an incubatorium for emerging viral diseases that could have severe global public health impacts.

The confirmed human case-rate mortality from the H5N1 avian flu strain of 2003/2004 (~ 70%) is seven times higher than that reported for the SARS virus, and roughly equivalent to that associated with recent outbreaks of the Ebola virus in central Africa and Nipah virus in Bangladesh. Demonstration of known changes in the virulence and infectivity of the H5N1 avian influenza virus and the apparent recent emergence of the SARS clearly demonstrate the importance of increasing our knowledge of the emergence of recombinant zoonotic viruses and the evolutionary dynamics of viral host/pathogen relationships. Recent experience with the H5N1 avian influenza virus and the genetics of the SARS virus has demonstrated that the host affinities and epidemiological characteristics of these zoonotic viruses may continue to change, and either one or both of these pathogens may become even more infectious and more virulent to both animals and humans within the foreseeable future.

Current evidence indicates that H5N1 avian influenza viruses with pandemic potential have now become endemic in domesticated duck populations in China and southeastern Asia, and may not easily be eradicated or even controllable for the near future. Although wild ducks, storks, and other migratory birds have been implicated as potential vectors and reservoirs for the H5N1 virus, evidence to date suggests that wildlife are more often victims than vectors of this potentially deadly disease of that is now known to infect birds, humans, and several species of wild and domesticated mammals.

Key words: Asia, origin, avian influenza, SARS, virus, zoonoses

Southeast Asia was one of the earliest centers of human agriculture, and the region has had a longer history of continuous, intensive agriculture than any other area on earth. The 7,000 year or more history of intimate association between humans, wildlife, and domesticated animals in southern China makes this area a fertile ground for the evolution and emergence of novel viruses of humans and domesticated animals, particularly influenza viruses capable of infecting poultry, swine, and/or humans. Unlike agricultural areas of the Middle East having civilizations of similar antiquity, these agricultural areas of China have

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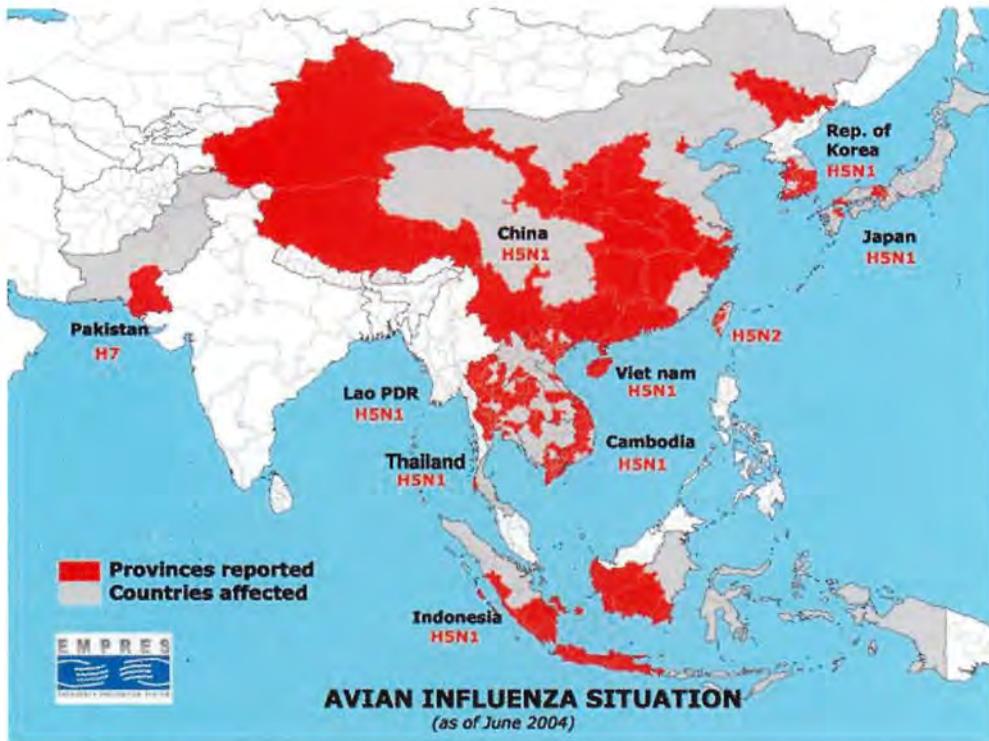


Figure 1. Avian influenza situation as of June 2004.

http://www.fao.org/ag/AGA/AGAH/EMPRES/Images/avian25062004_640x480.gif

a history of continuous occupation with a triad consisting of domesticated ducks—the natural host of the type A(H5N1) avian influenza—wild and domesticated swine, and humans. Recent experiences with the emergence of the SARS virus in Guangzhou and Hong Kong, the Nipah virus in Malaysia and Bangladesh, and the proliferation of a new and more dangerous zoonotic strain of the H5N1 avian influenza virus, demonstrate the importance of southeastern Asia as an incubator for emerging viral diseases that could have severe global public health impacts.

The still on-going pandemic of H5N1 avian influenza in Asia is absolutely unique and unprecedented in its virulence, rate of proliferation, geographic scope, and duration.^{1,2} As of early August 2004, new outbreaks of the H5N1 were being reported from Thailand, Malaysia, and Vietnam. Thailand has reported 16 laboratory confirmed cases of human H5N1 infections during the period between 1 January and 5 October 2004, four of which occurred during the month of September 2004. As of 5 October 2004, reported human case-rate mortality from the H5N1 virus in Vietnam and Thailand has been approximately 72 % (31 of 43 confirmed cases).³ Confirmed case-rate mortality for human infections by the H5N1 avian influenza virus in Vietnam and Thailand are as high or higher than those recorded for human cases of the Ebola virus in central Africa or Nipah virus in Malaysia and Bangladesh. The confirmed human case-rate mortality from H5N1 avian flu during the 2003/2004 outbreak has been approximately two times higher than that historically associated

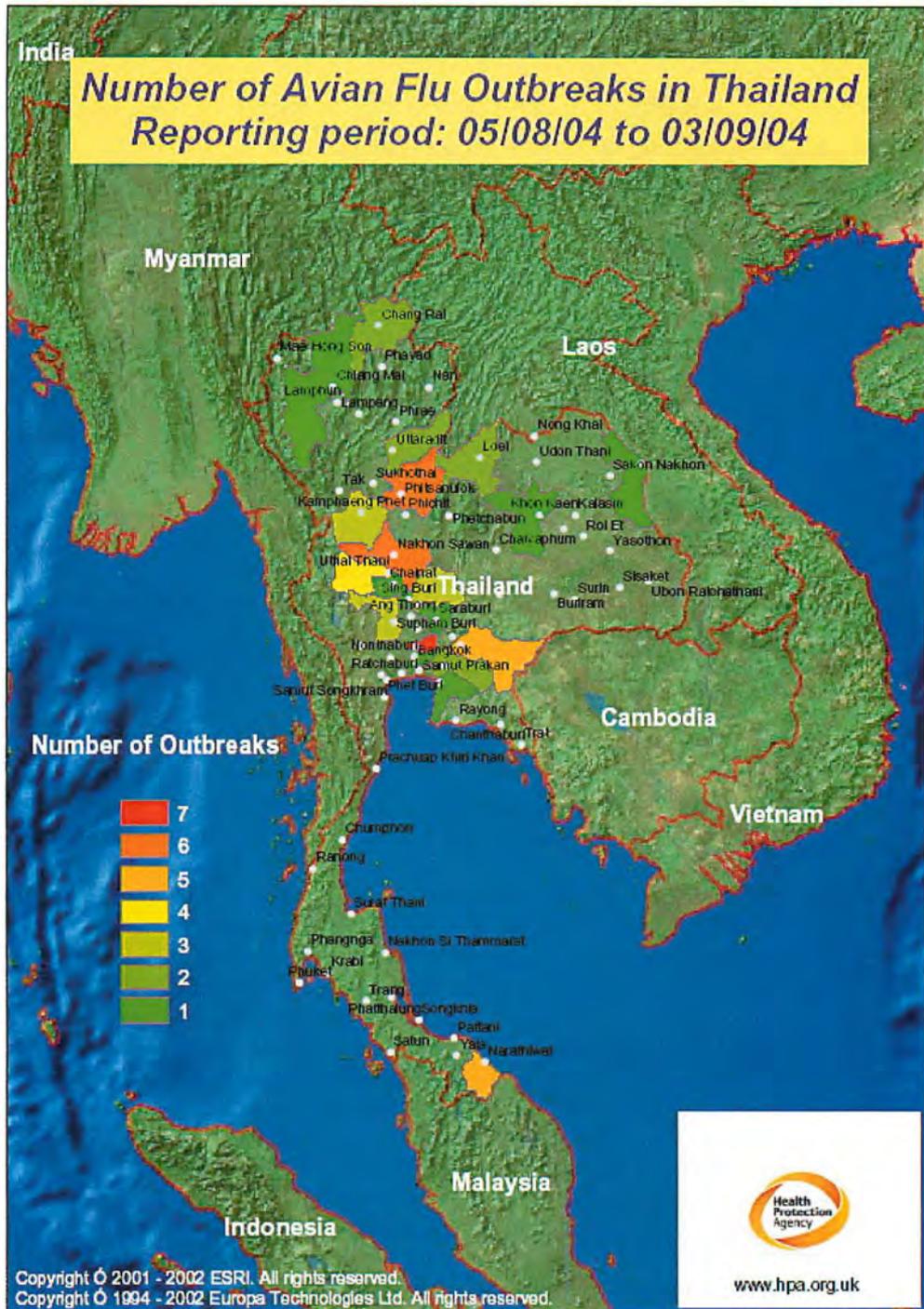


Figure 2. Porton Down map of reported recent Avian Influenza outbreaks in Thailand.

http://www.hpa.org.uk/infections/topics_az/avianinfluenza/pdfs/Thailand_outbreak_map0904.pdf

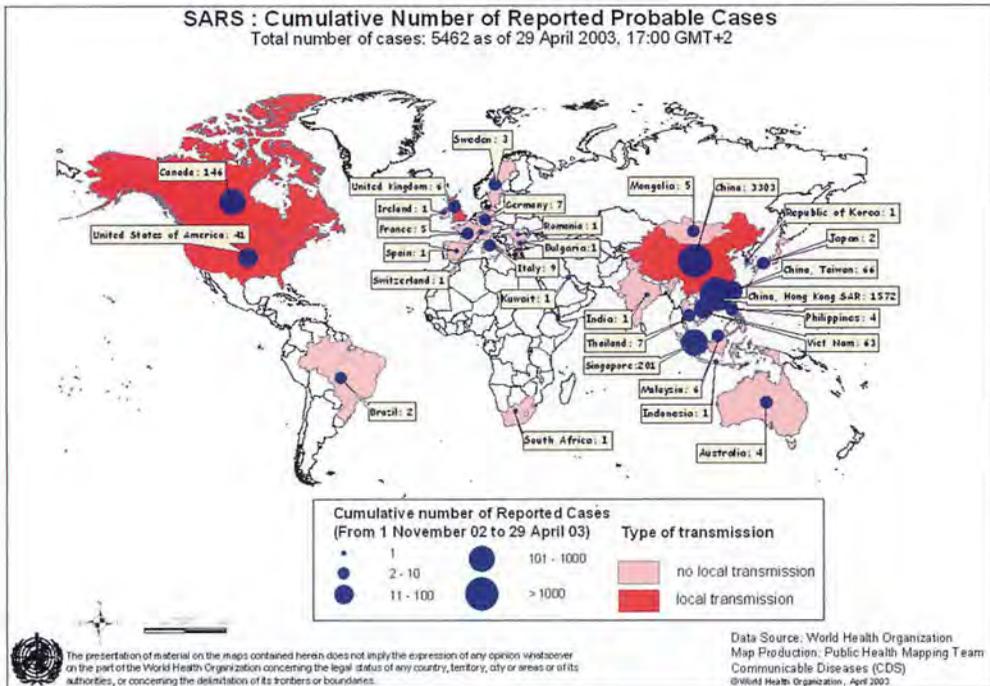


Figure 3. Worldwide distribution of SARS epidemic in 2003.

http://www.who.int/csr/sars/map-2003_04_29.gif

with smallpox *Variola major*,⁴ seven times higher than the confirmed death rate for the SARS coronavirus,⁵ and comparable to confirmed human case-rate mortality recorded from outbreaks of Nipah Virus in Bangladesh (60–74 percent)⁶ and Ebola virus in central Africa (50–90 per cent).⁷

The unusually large number of domesticated ducks dying from bird flu in southern China indicates the H5N1 virus circulating in 2003–2004 is a mutated strain that is also more virulent in birds and mammals than H5N1 strains encountered in previous years (L.L.M. POON, personal communication).⁸ The H5N1 strain circulating in 2003/2004 is not only more highly virulent in mammals than strains collected in previous years,⁹ but has reportedly caused fatal infections in a much broader range of mammal species than during previous outbreaks (e.g. domesticated cats, tiger, clouded leopard). U.S. and British scientists recently determined that the 1918 “Spanish” influenza virus estimated to have killed as many as 50 million people worldwide was actually an avian influenza-type virus, and not a swine influenza virus as reported by previous studies.¹⁰ The 1918 flu virus differs significantly in its genetic structure from the H5N1 avian flu virus currently circulating in Vietnam and Thailand, however, and the current H5N1 strain does not appear to possess the human-to-human contagion and transmission capability exhibited by the so-called “Spanish” influenza virus (a misnomer, as epidemiological evidence suggests the virus originally emerged in the United States).¹⁰

Current evidence indicates that H5N1 avian influenza viruses with pandemic potential have now become endemic in domesticated duck populations in China and southeastern

Asia, and may not easily be eradicated or even controllable for the near future.⁸ The new deadly and highly persistent strain of H5N1 avian influenza virus circulating in Thailand could pose continuing threats to public health, wildlife health, veterinary health, trade and tourism in southeastern Asia—and potentially around the entire globe—unless effective control measures for this dangerous zoonotic pathogen can be successfully developed and implemented in Thailand, China, Vietnam, Malaysia, Laos, Myanmar, and Indonesia. Although wild ducks, storks, and other migratory birds have been implicated as potential vectors and reservoirs for the H5N1 virus, evidence to date suggests that wildlife are more often victims than vectors of this disease.

Severe acute respiratory syndrome (SARS) is a deadly form of pneumonia caused by an apparently newly emerged mutated coronavirus, which the available evidence suggests is derived from an endemic Asian virus associated with one or more species of wild mammals, particularly mustelids, native to southern and eastern Asia. Coronaviruses (Coronaviridae) are a viral family known to cause infections in a wide variety of animals, including (among others) humans, pigs, cows, mice, cats, and birds. The SARS virus itself has been identified as a recently-mutated strain that originated through a 29-nucleotide deletion mutation of a closely-related coronavirus which has been isolated from several species of wild animals taken from live-animal street markets in mainland China (i.e., palm civet *Paguma larvata*, raccoon dog *Nyctereutes procyonoides*, ferret badgers *Melogale* spp.).¹¹ Domestic cats and domestic ferrets have been experimentally infected with the SARS virus,¹² and subsequent studies have reportedly discovered the SARS virus in foxes, voles, rats, and domestic cats.¹³

Chinese health officials reported new studies in April 2004 showing that testing of humans and wild animals has confirmed earlier suspicions that animals other than viverrids (civets) may be responsible for spreading SARS in humans. Indeed, the earliest known SARS victim was linked to possible infection from a domestic cat or a snake, rather than any wild mammal species.¹³ Researchers who traced the virus that causes SARS to the palm civet *Paguma larvata* identified antibodies to SARS in traders of live wild animals in southern China markets who had not developed symptoms of the disease.¹⁴ Tests on workers at wild animal markets in 16 cities in Guangdong Province found antibodies to the SARS virus in nearly 100 of the 994 animal traders exhibited, while SARS antibodies were found in only 4 of the 123 workers involved in the captive husbandry of the palm civet *Paguma larvata*, the species originally identified as the suspected source or reservoir for the SARS virus in China.^{14,15,16} Throat and anal swabs from animals at wildlife markets in Guangzhou subsequently confirmed SARS in raccoon dogs *Nyctereutes procyonoides* (15 of 15 samples positive), foxes (species uncertain: 3 of 5 positive), voles (Rodentia: Microtinae, 1 of 6 positive), and cats (*Felis catus*, 4 of 20 positive).¹³ The reported identification of SARS virus in “foxes” [*Vulpes* spp. ?] and voles (Rodentia: Cricetinae *gen./sp. incertae*, identified as “hedge-shrews” in English language sources) appear to be entirely new host records for canids and microtine rodents. The finding of SARS in cats and voles is not unexpected, however, as laboratory studies performed in 2003 showed that domestic cats¹² are susceptible to the SARS virus, and the SARS virus was reportedly confirmed from several rats trapped in the apartment of a SARS victim in Guangzhou, China.¹⁷

Two recently published genetic studies provide evidence that the SARS virus is a recombinant virus that incorporates genetic material from both avian and mammal viruses.^{18,19} Gene-sequence analyses indicate that the SARS virus genome is derived from a

recombination event between mammalian-like and avian-like parent viruses. Demonstration of past recombination events in the SARS coronavirus lineage indicates a high potential for rapid unpredictable mutational changes that could produce viruses capable of infecting both animals and humans, a potentially important challenge for public health management and drug and vaccine development.¹⁸ The location of the evident animal-avian recombination site in proximity to a region implicated as the human receptor site may have been directly responsible for the ability of the SARS coronavirus to shift from animals to humans.¹⁹

In January 2004, China ordered the closing of wildlife markets and the culling of an estimated 10,000 palm civets held in wildlife markets after genetic tests linked a virus isolated from civets to a new confirmed case of SARS case in Guangzhou, capital city of South China's Guangdong Province.²⁰ The Guangdong provincial government announced the ban on the breeding and sale of palm civets to prevent any possible spread of the apparent SARS precursor virus. Producers from central China who supply captive-bred civets to Guangdong markets are protesting the loss of markets and income caused by the new regulations. Civets and hundreds of other species of wild animals are sold in large numbers for use in food and medicinal products in Thailand, China, and other countries in southeastern Asia. Although China had banned the trade in civets and 53 other wild animals during April 2003, the ban was lifted in August 2003 after scientists were unable to confirm which animal species was the apparent source or reservoir of the new human SARS virus.²¹

Urban rats may prove have been the source of infection for the SARS case reported from Guangzhou, China in December 2003. *China Daily* reported that laboratory tests determined rats caught in the SARS victim's apartment were carrying the SARS virus,¹⁷ and although the report was not confirmed by government health authorities, a new campaign to extirpate rats was announced by the official news media at the same time this report was circulated by the local press. Local media in Guangzhou reported that the patient had been trapping rats that had invaded his apartment before he showed any SARS symptoms; the patient said that he had no known contact with the civet species identified publicly by the Chinese government as the probable source or reservoir for the disease.¹⁵ Rats have been hypothesized as a possible source for an outbreak in Hong Kong during March 2003.²² Should SARS become established in urban rat and cat populations, this disease could prove difficult or impossible to control or eradicate from Guangzhou, Hong Kong, or other large cities or metropolitan areas in southern China.

Although SARS virus evidently did not originate in rats, the current evidence seems to indicate that what we are witnessing and tracking at this moment is a significant evolutionary event involving the tentative early stages of the process whereby a newly-mutated viral pathogen, the SARS virus, establishes a host-pathogen symbiosis with a new reservoir host species (such as rats, cats, humans, etc). If we are fortunate, the SARS virus in it's current form may not be able to establish itself as a self-sustaining zoonotic pathogen within urban rat populations, and the disease will occur in urban rats only as a transient and dead-end secondary host. In this case the closing of wildlife street markets to the sale of potential wildlife reservoir hosts (raccoon dogs, palm civets, etc.)²³ by the government of China could successfully prevent subsequent outbreaks.

The definitive host reservoir for the SARS pathogen is still unknown at the present time. It cannot be ruled out whether virus aerosols derived from mechanical transmission or urine/fecal contamination by rats (*Rattus rattus* and/or *R. norvegicus*,²⁴ rather than

aerosolized virus from a contaminated toilet ventilation system,²⁵ may have been the driving mechanism for proliferation of the March 2003 SARS outbreak in the Amoy Gardens, Hong Kong. It seems possible that if the intensive rat eradication efforts undertaken at the sites in Guangzhou or Hong Kong where SARS outbreaks occurred were successful (or nearly so), it may still be possible that latent SARS infections are circulating in such a very small number of individual rats that the disease may not be evident even if it is in fact still present in urban rat populations at these sites. It is extremely important that we investigate and evaluate any and all potential reservoirs and transmission mechanisms for the SARS virus.²⁶

Recent events have shown biosecurity precautions and access for laboratory cultures of the avian influenza, the SARS virus, and other potentially lethal pathogens must be both increased and rigorously enforced. Laboratory exposures have been blamed for a SARS case in Singapore that occurred in September 2003, a SARS case in a researcher from Taiwan during December 2003, and an April/May 2004 outbreak of SARS in China that resulted in at least four confirmed human SARS cases that precipitated the resignation of the chief of China's Center for Disease Control where the incident occurred. Nonetheless, the confirmation of a case of apparent laboratory-acquired SARS in a senior scientist in the Institute of Preventive Medicine, National Defense University in Taipei who recently traveled to a medical conference in Singapore sparked a new wave of SARS surveillance activity in mainland China, Taiwan, and Singapore,²⁷ and may have contributed to the early detection by Chinese officials of a new SARS case in Guangzhou on 26 December 2003.²⁸ There were also two similar incidents involving the Ebola virus during the first five months of 2004, one of which resulted in the death of a Russian researcher at the Vector-State Research Center of Virology and Biotechnology.^{29,30}

Thai government officials have suggested that migratory birds were the cause of avian flu outbreaks in Thailand, and Cambodian agricultural authorities announced an outbreak of H5N1 avian influenza in Cambodia discovered in September 2004 might have been caused by wild ducks frequenting a pond near the farm where the outbreak was discovered. Similar claims were made recently by South Korean officials who said that results of a 9-month study on the origin of widespread avian influenza indicated that domesticated ducks that were the source of a widespread outbreak in South Korea in December 2003 may have been infected by migratory wild birds. A report issued by the government of Japan in June 2004 also implicated—but could not unequivocally identify—migratory birds as the source of the H5N1 bird flu outbreak in Japan during January and February 2004, since genetic analyses showed that the virus in Japan was identical to that found in South Korea.

Information collected by the author on the reported incidence of avian flu in southeastern Asia during the period from October 2003 through October 2004 indicates that the observed pattern of H5N1 avian influenza outbreaks during the past year follows a south-to-north trajectory through the fall and winter months that appears to be incompatible with a migratory bird vector hypothesis. The available data now show that the earliest known outbreaks of the current H5N1 avian influenza pandemic began in Indonesia, Thailand, and Vietnam during October–November 2003, followed by subsequent reported outbreaks in Korea (December 2003), Japan (January 2004), Cambodia (January 2004), and China (January 2004). The available evidence does not show any evidence of correspondence between the geographic and temporal distribution of reported outbreaks in poultry and the known migratory patterns of wild bird populations in the eastern Asia. Migratory birds

cannot be linked to outbreaks in multiple sites located along or near major migratory routes for any given species or class of migratory birds (e.g., waterfowl, raptors, passerines, or shorebirds), and the observed outbreaks in poultry do not appear to correspond either spatially or temporally with migration patterns typical of wild birds in eastern Asian landscapes.

The public health effects and economic impacts of the current avian influenza epidemic necessitate a thorough and exhaustive investigation of the relative roles of domesticated poultry and wild birds in the transmission and persistence of avian influenza in Thailand. In order to be effective, however, these efforts will require increased cooperation and coordination between and among scientists and government officials in Thailand and other countries in Southeast Asia, and between international veterinary health officials and public health officials and their Thai counterparts.

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