Epidemiology of H5N1 avian influenza

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Abstract

High pathogenic (HP) H5N1 avian influenza (AI) infection has been reported in domestic poultry, wildlife, and human populations since 1996. Risk of infection is associated with direct contact with infected birds. The mode of H5N1 spread from Asia to Europe, Africa and the Far East is unclear; risk factors such as legal and illegal domestic poultry and exotic bird trade, and migratory bird movements have been documented. Measures used to control disease such as culling, stamping out, cleaning and disinfection, and vaccination have not been successful in eradicating H5N1 in Asia, but have been effective in Europe.

Keywords: Orthomyxoviridae; Highly Pathogenic Avian Influenza; Poultry diseases; Pandemic surveillance; Wild aquatic birds; Distribution; Spread

Résumé

Depuis 1996, des cas de grippe aviaire H5N1 hautement pathogène (HP) ont pu être observés chez les volailles domestiques, les oiseaux sauvages et les humains. Le risque de transmission est associé au contact direct avec des oiseaux infectés. La manière dont le virus H5N1 s’est propagé de l’Asie à l’Europe, l’Afrique et l’Extrême-Orient n’est pas claire ; des facteurs de risque tels que le commerce illégal d’oiseaux exotiques et de volaille domestique, et la migration des oiseaux ont été attestés. Les mesures mises en place pour contrôler le virus, notamment l’abattage, le nettoyage, la désinfection et
la vaccination, se sont révélées insuffisantes pour éradiquer le virus H5N1 en Asie, mais ont porté leurs fruits en Europe.

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Mots clés : Volaille ; Maladies aviaires ; Gibier migratoire ; Grippe aviaire hautement pathogène ; Orthomyxoviridae ; Surveillance de la pandémie ; Épidémiologie

1. Introduction

Avian influenza viruses (AIV) are enveloped, single stranded negative sense RNA viruses that belongs to the Orthomyxoviridae family [1]. Within the nucleocapsid, the virus contains eight segments of RNA that code for ten proteins, and is susceptible to high rates of mutation since replication is RNA polymerase dependent. Mutation can also occur through reassortment, when a cell is co-infected with two different AIVs that exchange RNA segments when packaged into the nucleocapsid and are lysed from the cell, giving rise to new viruses [2–4]. AI viruses are characterized by the nucleoprotein and matrix protein antigens, which are type A. Type A influenza viruses can be highly pathogenic to both humans and birds and can infect a broad range of hosts [1]. AIV are subtyped by characterization of hemagglutinin (HA) and neuraminidase (NA) glycoproteins, located on the outer surface of the envelope. Sixteen HA and nine NA subtypes have been identified [1,4,5]. AIVs can also be classified by their pathogenicity in naïve chickens. Low pathogenic (LPAI) viruses mainly cause respiratory illnesses in poultry and generally low mortality. Highly pathogenic (HPAI) viruses cause systemic disease, often resulting in high mortality in turkeys and chickens [1,4]. H5 or H7 AIV can be either LP or HP, all other known HA subtypes have only LP forms.

HPAI H5N1 began circulating in Hong Kong in late 1990s, and recently has spread beyond Asia into Europe and Africa. H5N1 was first isolated from a flock of sick geese in the Guangdong Province of China in 1996 (A/Goose/Guandong/1/96) [6]. In May 1997, a 3-year-old boy in Hong Kong was infected with H5N1 and subsequently died from respiratory failure. By the end of 1997, 18 people were infected and all live bird markets (LBMs) were closed and depopulated. Reports of human cases ceased when LBMs were closed, early epidemic investigations associated human cases and their exposure to the LBM system in Hong Kong. The HA from human cases and subsequent H5N1 outbreaks in Asia are genetically related to A/Goose/Guandong/1/96. The lineage of the 2003–2006 H5N1 epidemic is genetically rooted from these isolates in 1997, A/Ch/HK/1997/H5N1 and is referred to as the Z-genotype [6,7]. The Z-genotype of H5N1 has emerged as the dominate strain that has spread in Southeast Asia, China, and Europe [7].

Since 1997, isolations of H5N1 HPAI (referred to as H5N1) has continued sporadically in Hong Kong, China, and Southeast Asia in domestic and wild birds. Human cases of H5N1 resurfaced in Vietnam in 2003, which began another epidemic in Southeast Asia with sporadic cases in Europe, Africa, and the Middle East. Since October 2003, there has been a 60% case-fatality rate with 157 of the 261 documented human cases dying [8]. In addition to humans, domestic poultry and waterfowl, the infected host species for H5N1 has expanded to wild birds, canines, felines, swine and...
mustelidae [9]. The far reaching effects of H5N1 have not only adversely affected domestic bird and human population health, but also poultry industries on a global scale [10,11]. Many control policies for prevention and response to H5N1 outbreaks have been implemented and surveillance has increased even in countries that have not had a case. There have been three waves of this epidemic with respect to reports of human cases so far. In this manuscript, we will review the course of events since the discovery of the Asian strain H5N1 virus in 1996, the research, modes of disease transmission and control and prevention strategies in use.

2. Distribution (space and time)

2.1. Prior to wave I: 1999–February 2003

Asia/SE Asia: Isolates of H5N1 from commercial geese and ducks during this period were from subclinically infected birds. In May 2001, a severe increase in mortality in chickens due to H5N1 was reported in Hong Kong. An immediate decision was made to cull over a million chickens within the same month, resulting in no further reports of poultry cases that year [12]. However, outbreaks have occurred in poultry in Hong Kong every year since 2001, usually in the winter months, coinciding with an increase in imported poultry to meet the demand due to Lunar New Year activities [13]. HPAI outbreaks in wild birds are rare; however, cases of HP H5N1 in wild bird have been discovered through surveillance. In late 2002, high mortality rates were observed in free-flying wild waterfowl in two parks in Hong Kong. Isolates of HP H5N1 from Kowloon Park were found to have the genetic marker consistent with prior adaptation in land-based poultry, whereas the H5N1 isolates from Penfold Park were missing this genetic marker on the NA gene [14]. Laboratory results from these isolates suggest many genotypes of H5N1 were circulating among wild birds in Hong Kong.

Surveillance of AI in waterfowl during 1999–2002 in Mainland China yielded 21 H5N1 isolates from apparently healthy ducks in Southern China [15]. Experimental inoculation trials using these isolates demonstrated viral shedding from trachea and cloaca in ducks and caused death in inoculated chickens within 8 days [16].

In 2001, HP H5N1 was isolated in South Korea from frozen duck meat imported from Mainland China; however, no subsequent cases of H5N1 were detected in South Korea [17].

During 2001, surveillance in urban LBMs in Hanoi, Vietnam yielded several subtypes of AIV, including an H5N1 isolate from an apparently healthy goose. Genetic analysis showed the HA gene was closely highly related to those from poultry isolates in Hong Kong; however, the NA gene did not present with the common trait of adaptation found isolates from land-based poultry and humans [18]. These findings were published after human and poultry cases were reported in Southeast Asia in the summer of 2003.

In February 2003, three family members visiting Mainland China in the Fujian province, were treated for severe respiratory distress due to H5N1 infection after returning to their home in Hong Kong SAR. No other human cases were reported in Hong Kong SAR or Mainland China at that time [19].
2.2. Wave I: December 2003–March 2004

Early in the epidemic, it was weeks between the detection of disease and confirmation of H5N1 infection. For example, in December 2003 and January 2004, cases of H5N1 were reported in Vietnam, which was the first country to report H5N1 as a cause of mortality and respiratory distress in humans since 1997. However, severe respiratory distress that required hospitalization occurred in late October 2003 and these cases were later confirmed as H5N1 cases in January, 2004. Soon after case reports from Vietnam, Thailand also confirmed human and poultry cases of H5N1. Unlike previous reports of infected poultry from the 1997 outbreak in Hong Kong SAR, mortality in infected poultry in Vietnam and Thailand was high, nearly 100% in infected poultry flocks [20].

In December 2003, two tigers and two leopards in a Thai zoo died following feeding with fresh chicken carcasses from a local slaughterhouse in Suphanburi, where chickens were dying with respiratory and neurological signs [21]. H5N1 was isolated from the lung tissues of reported cases of H5N1 causing severe respiratory disease and mortality in non-domestic felids.

During the same month, Korea reported outbreaks of H5N1 on 19 commercial poultry farms, 14 of which occurred within 2 weeks of the index case. The epidemic ended in March 2004 [22]. Magpies were frequently observed by the owner of an infected farm entering the area where chicken feces were dried and disposed [23]. Dead magpies on the farm were found to be infected with H5N1.

From December 2003 to March 2004, an outbreak of H5N1 was reported in three chicken farms and in a number of pet chicken flocks in Japan [24]. The farms were between 150 and 250 km away from each other, and dead crows found near infected farms were also found to be infected with the same genotype H5N1. The isolates from this outbreak were all genetically similar, but very different from the genotypes that had spread across Southern China, Southeast Asia, Russia and Europe. The isolates were similar to another genotype from Guandong Province in Southern China [24]. Genetic studies conducted on the isolates from Japan and Korea show that the genotypes of H5N1 that caused outbreaks in both countries were very similar to each other [25]. Speculation that wild bird migration was the source of infection could not be substantiated by surveillance information; there were no isolations of H5N1 from over 5000 wild migratory birds sampled in Korea [22].

In February 2004, Hong Kong SAR and Indonesia reported cases in poultry, but not humans. By the end of March, there were 34 human laboratory confirmed cases, 23 of which were fatal. Between March and June 2004, no human cases of H5N1 were reported. Vaccination for H5N1 in commercial domestic poultry was implemented as a control strategy in Mainland China, Hong Kong SAR, and Indonesia [26].

Reported poultry cases were generally backyard poultry in rural areas, usually not kept indoors or within confined areas. Over 80% of poultry in Southeast Asia, and 60% in China are backyard, free-range flocks [27,28]. Over 100 million birds were culled in affected countries; however, these efforts did not stop the next wave of HP H5N1 infections in these and others countries.
2.3. Wave II: June 2004–November 2004

In June and July 2004, China, Indonesia, Thailand, and Vietnam reported a recurrence of H5N1 in poultry. Japan and Korea were declared H5N1-free, and did not report any cases during waves II or III. Compared with wave I, wave II affected fewer countries and cases were reported from fewer municipalities from infected countries than during wave I [29].

In August 2004, Malaysia reported poultry cases in nine villages. No human cases were reported. Poultry cases were reported from Malaysia through November 2004. Surveillance in areas surrounding the outbreak within 10 km led to finding H5N1 among poultry, which were promptly culled [29–31].

Less than 10 human cases in Vietnam and Thailand were reported between July and October 2004; nearly all of which were fatal. An unpublished oral report of H5N1 isolation from pigs in China is noted in the WHO H5N1 epidemic timeline; however, no further information about size, location, or clinical signs of the outbreak is known.

In October 2004, another H5N1 outbreak in tigers at a Thai zoo was reported in which 147 died or were euthanized. Tigers that died from infection had respiratory distress and severe pneumonia [32,33]. There was evidence of tiger-to-tiger as well as likely infection after the consumption of AI-infected chicken carcasses as the modes of transmission.

Two eagles, hidden in tubes and illegally imported into Brussels from Thailand, were found in October to be infected with H5N1. No clinical signs were observed in the birds, which were later euthanized. The man who smuggled the birds did not have symptoms and tested negative for H5N1 [34].


Two months later, human cases were reported in Southeast Asia, marking the beginning of the third H5N1 epidemic wave. Since then, human cases have been reported every month in Asia, Eastern Europe, Africa and the Far East. In Asia, human cases in Indonesia were first reported in July 2005, and continued well into the winter of 2006 [35]. The case-fatality worldwide has remained at approximately 60%; however, the human case-fatality rate in Indonesia is higher, at about 77% [8]. China reported the first human cases during this wave of the epidemic and poultry cases in 9 provinces, followed by culling 20 million and mass vaccination in all birds to control the epidemic [13,36]. In February 2006, Malaysia, which had been declared disease free since late 2004, reported an H5N1 outbreak at a free-range poultry farm.

In October 2005, 276 dead songbirds that were being smuggled from Mainland China by cargo ship were intercepted in a Taiwan harbor and found to be infected with H5N1. This event, combined with the findings of infected eagles in Europe, raises concerns and awareness of this mode of disease spread [37].

During this wave of the epidemic, the number of known susceptible species, including wild birds, grew. In July 2005, three captive civets, which had clinical signs similar to those in infected felines, died of H5N1 infection in Vietnam [38]. This was the first report of H5N1 in this species and was a cause for concern in Asia, as civets are sold in live animal markets or wet markets, in which exposure to wet markets was also a risk for human infection of sudden acute respiratory syndrome (SARS), a zoonotic severe respiratory...
disease that originated in China. The source of infection remains unknown since animal surveillance within a 10 km area did not find any animals infected with H5N1. No other reports of H5N1 infection in civets have been made since July 2005 [38].

During April 2005, over 6000 wild migratory birds died at Qinghai Lake in Central China. The dead birds were mainly bar-headed geese, gulls, shelducks, and cormorants. H5N1 virus was the only pathogen isolated. Two months later, China reported an outbreak of H5N1 in domestic poultry in Xinjiang AR, located at the northwest border of China with Kazakhstan and Mongolia [39]. Prior surveillance at various sites of live migratory waterfowl, including bar-headed geese, did not result in the isolation of H5N1 in 493 samples taken from June 2004 to May 2005 [29,40]. In experimental studies of the H5N1 isolates from dead birds at Qinghai Lake in April, mortality in chickens and mice was greater than that from experiments using previous H5N1 isolates [41]. The authors concluded this was a new variant of H5N1, more virulent than earlier H5N1 isolates from ducks in China.

In July 2005, poultry and dead migratory bird H5N1 cases were detected in Western Siberia. In the following month, Kazakhstan and Tibet AR also reported both poultry and migratory bird H5N1 cases. Dead H5N1-infected migratory birds, bar-headed geese and whooper swans, were also reported from two lakes in Mongolia [42]. No isolates of H5N1 were found from 774 samples taken from live whooper swans, shelducks, bar-headed geese, and black-headed gulls [43]. The last report of H5N1 in Russia was in August 2006 in domestic pigeons and poultry [44].

In October 2005, H5N1 poultry cases were reported in Turkey and Romania, and infected mute swans were reported in Croatia and Hungary [45]. The first outbreaks of H5N1 in Turkey were in commercial poultry farms in the western region of the country followed by human cases in the eastern region of the country in December. Human cases occurred in children under the age of 15 years who had extensive exposure and direct contact with sick or dead poultry. It is likely that human cases emerged because of the close human-poultry contact arising when poultry were brought indoors during cold weather [46].

In late October 2005, H5N1 was isolated from sick birds at a zoo in Jakarta. Zoos in Indonesia were closed to test all birds within the zoos, as well as clean and disinfect the premises [42].

In November 2005, a single dead flamingo in Kuwait was found to be infected with H5N1; however, no other cases were reported in the country. All poultry and human cases throughout December occurred in Turkey, China and Southeast Asia. In February 2006, backyard flocks infected with H5N1 were reported in Iraq and Nigeria. Among reported domestic poultry cases in Iraq, domestic cats were also found to be infected with H5N1 [47]. Two human cases in Iraq were reported, a 15-year-old girl and her 39-year-old uncle. Dead infected swans were also found in Iraq and Egypt in February. Human cases were reported in Egypt in March, and in April a countrywide outbreak was reported in commercial poultry flocks [48]. A month later, the first human case in Azerbaijan was reported along with poultry cases and isolation of H5N1 in a dead wild duck [49]. Egypt remained the only African country to report human H5N1 cases, until May 2006 when a human case was reported in Djibouti. In March through May 2006, H5N1 poultry cases were reported in Afghanistan, Pakistan, Jordan, and Israel and in other North African countries of Djibouti, Niger, Burkina Faso, Cameroon, Sudan, and Cote d’Ivoire.
During February and March 2006, dead H5N1-infected swans were also detected in Bulgaria, Greece, Italy, Austria, Hungary, Germany, Slovakia, Bosnia-Herzegovina, Slovenia, Poland, Czech Republic, Denmark, and Serbia-Montenegro. Infected wild ducks were also found in Switzerland and Sweden in January and March, respectively [50]. In February, an infected wild duck was found and shortly after, turkeys on a commercial farm were also reported to be infected with H5N1 in France. In Germany, dead domestic cats, and a severely ill stone marten were found to be infected with H5N1 in March on Ruegen Island, where many wild birds were also found to be infected with H5N1 [9]. By April 2006, dead infected swans were reported from the UK and Germany reported an isolated outbreak of H5N1 on a large farm of turkeys, geese and chickens [9]. Outbreaks of H5N1 in poultry were also reported from Denmark and Albania in June and March, respectively [50].

2.5. June 2006–December 2006

From June to December, most human cases of H5N1 were reported from Indonesia (24 cases), followed by Egypt (4), Thailand (3), China (2), and Iraq (1). Outbreaks among poultry were more widespread, as reports continued from Northern Africa, China, and Southeast Asia [51]. Indonesia continued to report human and poultry cases. In November and December, South Korea reported a reemergence of H5N1 infection in poultry farms. The mode of transmission and spread are still under investigation.

3. Host species

Poultry-Galliformes, such as chickens, turkeys, peafowl, and quail are susceptible to AI. Poultry surveillance in Hong Kong and Vietnam of LBMs continually has yielded isolates of HP H5N1; however, the samples are often from clinically healthy birds [12,18,52,53]. This is in contrast with experimentally HP H5N1-infected chickens, which present with severe respiratory distress within 24 h, and die within 48 h. Laboratory inoculation in quail using HP H5N1 isolates caused death within 2–3 days [54]. Neurological signs are observed in experimentally inoculated geese and emus [55]. Ducks generally do not show clinical signs when infected with LPAI. An experiment inoculating ducks with H5N1 isolates yielded mixed results. Ducks inoculated with H5N1 genotype CK/Yamaguchi/04, HK/483/97, or a recombinant HP H5N1 did not show clinical signs, whereas ducks inoculated with Dk/Yokohama/03 had neurological signs [56]. In an inoculation experiment using H5N1 isolates from 2003 to 2004 in ducks, the ducks did not show clinical signs or mortality with the exception of one isolate of H5N1 from a human in Vietnam [16].

Wild waterfowl—In general wild waterfowl and shore birds are the reservoirs of LPAI, and can replicate and shed these AIVs without signs of disease. When infected with HPAI, and in the case of HP H5N1, results from surveillance show that there are differences in clinical signs of infection in wild birds from the same order and that signs of disease are genus specific. Some birds, like mallard ducks, can carry and shed HP H5N1 without clinical signs for long periods of time, whereas other migratory birds, such as geese, muted swans, and herons often die from infection [14,16].
Humans—Case definitions are based on hospitalized patients, which include those with extremely high fever, influenza-like symptoms involving the lower respiratory tract, gastrointestinal symptoms and encephalitis with exposure to, or a recent history of handling, poultry [57]. Human infection is rare; however, the reported case-fatality is high. Early reported case-fatality in 2003 was approximately 50%; however, more recently reported case-fatality in Indonesia was approximately 80%. These findings should be viewed with caution, since not all cases are confirmed while others may not be reported at all. A study of poultry workers in Hong Kong reported that approximately 10% of the workers were found with antibodies to H5N1, though none presented with any signs or symptoms of disease [58]. Government workers, who participated in the 1997 epidemic response, had a 3% seroprevalence. Surveillance in humans is often in response to a severe respiratory case discovered in a healthcare facility or household and therefore the true prevalence of the population with subclinical infection of HP H5N1 is unknown. Familial case-clusters from Indonesia analyzed in 2006 did not result in the identification of index cases within families but found that only blood-related family members were infected with H5N1, even though there was no apparent difference in exposure between blood-related and non-blood-related family members. These findings may suggest a genetic predisposition to infection with H5N1 [59].

Other mammals—A cause for concern for further risk of disease spread is the infection of felines with H5N1. In Thailand, tigers fed infected poultry carcasses became infected and died [60]. Tiger-to-tiger transmission was evident and feline-to-feline transmission has been confirmed experimentally [32,61]. Dead cats were found nearby confirmed H5N1-infected premises housing domestic poultry, and H5N1 was isolated from the gut, stool, and trachea in the cats [47]. Though studies have shown that human influenza subtypes can infect pigs, there is no evidence of adaptation of H5N1 in pigs prior to circulation in human populations. During the current epidemic, there has been an unofficial oral report of an isolated infection in pigs in China, and a single report of H5N1 in pigs in Indonesia [39]. Eight of 3175 (0.25%) pig sera samples from Vietnam and Thailand were positive for antibodies to H5N1. Experimental infection of pigs did not produce transmission between infected and susceptible pigs [62]. Miniature pigs inoculated with three genotypes of HP H5N1 did not present with clinical signs and 2 of the 3 H5N1 genotypes did not replicate. A recombinant H5N1 was the only genotype that caused seroconversion in the inoculated pigs [54].

Canines were identified as another possible host for HP H5N1 from surveillance studies in Thailand [63]. Outbreaks of influenza in canines have occurred before and the subtypes were found to be closely related to influenza circulating among equines [64,65]. Though in previous canine influenza outbreaks infected greyhounds presented with respiratory signs and mortality, no reports of any signs of H5N1 infection have been published. There are no further cases from surveillance of H5N1 infection in dogs from other countries, nor has exposure to infected dogs been linked to transmission to other species.

4. Modes of transmission

Evaluation of isolates collected from surveillance in Hong Kong SAR and Mainland China LBM concluded that LBM provide an environment for AIV reassortment [12,66].
Birds sold within the LBM system in Asia are at high risk for transmission of diseases since there are high rates of co-mingling for different species of birds from many different flocks. A case-control study conducted in 1997 to determine risk for H5N1 infection found a statistically significant association with exposure to LBMs, but not with the preparation or consumption of poultry [67]. Since 2003, poultry-to-human transmission of H5N1 has been found to be associated with direct contact with sick poultry, while there is limited evidence for human-to-human transmission among family members [68,69]. A matched case-control study was conducted in Vietnam in 2004. The authors reported that exposure or contact with sick or dead poultry within the house or neighborhood and no indoor water source within the household were statistically significantly associated with H5N1 infection [70]. Though LBMs or live animal markets in general can pose a risk for AI infection, LBM exposure has not been associated with human cases during the current wave of the H5N1 epidemic.

Another route for possible spread of H5N1 across national borders is illegal trade and transport of infected poultry or exotic birds. In some counties with H5N1 cases, where the demand for poultry is high, despite known risks of H5N1 transmission, poultry is transported illegally. Authorities in Vietnam estimate up to 70% of poultry that are illegally transported from China, go undetected [71]. Quantification of such practices and their association with outbreaks in any country, however, has not been documented. There are countries that have reported H5N1 infection in poultry in which infections are not associated with migratory bird movements and did not report poultry trade with other reported infected countries. This has led some researchers to suspect illegal trade of poultry or poultry products as a source for H5N1 outbreaks [36].

Generally, wild waterfowl and shorebirds are the reservoir hosts of LPAI viruses. It remains a debatable issue among AI and wildlife experts of the capability and level of risk for long-distance transmission of a poultry-adapted virus, like HP H5N1, from infected wild birds [72]. Poultry cases in Thailand were largely associated with rice patties and free-grazing ducks in the area [73]. The authors suggested that infection in domestic poultry was due to the co-mingling of wild waterfowl and domestic ducks arising from this type of agricultural practice. Poultry H5N1 outbreaks in Russia, Kazakhstan, and Turkey (Baltic Sea) all correlate in space and time with migratory bird movements [72]. Dead wild bird infected with H5N1 in European countries have often been followed by isolated H5N1 poultry cases, further strengthening the suspicion that infected wild birds have spread H5N1. Strong evidence to support the claim that wild bird movements spread disease across Russia into Europe and Africa is difficult to find. Most isolations of H5N1 were obtained from dead or ill wild birds and it is not possible to determine if these species of birds have transmitted H5N1 to poultry. It is likely, through findings from experimental studies, that ducks are subclinically shedding virus and likely spreading infection, not only to poultry, but also susceptible wild birds, such as swans, geese, and herons [16,56]. Surveillance in Africa of wild birds has not yielded H5N1 [74]. Migratory birds that have flyways through China and Southeast Asia also share their paths with Australia. So far, there have not been any reports of H5N1 infections in Australia. Migratory flyways are also approximations; all flyways for all migratory bird species are unknown and some researchers think that assumptions of migratory bird spread is premature based on available data [75]. Wild bird surveillance in Hong Kong continues to find infected wild birds;
however, there have not been any reports of poultry or human cases from Hong Kong since 1997 [76].

There is no evidence that cats can spread disease to other species, including humans. There have been no observations of human H5N1 infection from exposure to infected cats [70]. However, the discovery of new host species and a lack of evidence of their role in disease spread should not be disregarded when assessing transmission risk. The effects of early knowledge about the possibility of pigs as the mixing vessel for adaptation for disease in humans and changes in biosecurity and farming practices elsewhere in the world is immeasurable. Human risk for H5N1 infection has been strongly associated with poultry handling but not with exposure to infected pigs.

5. Control measures

Infected countries have implemented varying degrees of control measures of stamping out, restrictions on poultry movement, cleaning and disinfecting, and vaccinating poultry [77]. No control measure alone has been successful in eradicating H5N1, and the measure of success of any one activity is largely based on overcoming the obstacles that can prevent it from being carried out [27].

Stamping out is a control measure that includes culling infected animals and animals that have had contact with infected premises or are located close to an infected premises [78]. H5N1 poultry cases since 2003 have largely been backyard or village-raised birds. Rural villages are dependent economically on poultry for food and income, and in some countries a culling program does not include compensation for their losses. A researcher reported poor compliance attitudes in Cambodia, where there was little incentive for reporting ill or dead poultry to the government as there was no compensation for their losses [79]. In Thailand, where some compensation was available for stamping out, implementation of control measures were difficult because most of the poultry cases were backyard poultry and there is a limited number of epidemic response personnel [33].

Restriction of poultry movements within and outside restricted areas can be difficult to enforce, given other difficulties such as a demand for poultry meat and the scope of illegal activities. An illegal shipment of H5N1-infected songbirds was caught in Taiwan even though the punishment is up to 3 years of imprisonment and a fine 4400 USD [37]. Incentives to prevent illegal bird/poultry activities have not been successful in hindering the illegal movement of birds.

Cleaning and disinfecting premises requires removal or disposal of all potentially contaminated materials. The improper disposal and handling of carcasses can further spread disease. Disposal of dead birds off-site was identified as a major risk factor for the early spread of HPAI during an outbreak of LP H7N2 in Virginia [80]. The FAO recommends burial or composting contaminated carcasses on-site; which requires space, equipment and expertise [78].

Vaccination of poultry and wild birds as a sole disease control measure has never been effective. China and Indonesia use vaccination as a control measure and yet continue to report human and poultry H5N1 cases. An illegal hatching of ducklings was found in Vietnam when all the ducks died of H5N1 infection [81]. These birds were not vaccinated.
against H5N1 because of their illegal status. Therefore, two problems with vaccination in countries where a large proportion of poultry is backyard poultry are that illegally moved birds are unlikely to be vaccinated legally, and vaccine dissemination is often difficult. Much of the poultry in the EU countries that did not have a massive outbreak in poultry was in commercial settings where there are more incentives for those raising poultry to comply with government plans. In most of these countries, there were few isolated cases of H5N1 in human and domestic poultry populations; however, it is likely not completely due to mass vaccination of poultry. The EU approved the limited use of vaccines in a few countries, such as France, where limiting outdoor exposure for domestic geese and ducks was reportedly not feasible [82]. Even countries that have reported control policies such as culling and restriction of movement still face the challenges of compliance, especially countries with large rural populations.

Education programs to prevent disease have proven difficult to disseminate in Southeast Asia. One study to assess the effects of an educational campaign in Thailand to reduce the risk of human H5N1 infections found that the campaign had little effect on changing poultry handling behavior [83]. One researcher suggested that these attempts were unsuccessful because of the lack of available alternatives for poultry handling [84]. Education programs are even difficult in places where information is easily attainable. A phone study (N = 805) in Hong Kong to assess the perceptions and knowledge of H5N1 transmission was conducted in November 2005. The results conclude that much inaccurate information regarding the routes and risk of transmission still circulate among the population of the first H5N1 epidemic [85]. Many respondents believed that H5N1 could be transmissible via long-distance airborne transmission (35.8%) and that it was a vector-borne disease transmissible by insect bites (48.0%). Residents of Hong Kong have lived with the knowledge of H5N1 longer than any other country and yet, many of the people have misconceptions about transmission and risk.

6. Discussion

Over the last 3 years, it is interesting to note that, with the exception of Indonesia, H5N1 has not been isolated south of the Equator. Surveillance efforts in Australia and South Africa have yet to find H5N1 in wildlife or land-based poultry. It is also interesting to note that these areas are not wintering grounds by migratory wild birds that summer in Europe or Asia [36]. That is not to say that areas such as Southern Africa are not at risk for HPAI epidemics. During the last year, there was an outbreak of HP H5N2 in South Africa and Zimbabwe in land-based poultry [86].

There were few isolates H5N1 from live wild birds during this epidemic [14,75,76]. Surveillance of live wild birds would be useful in finding reservoirs for HPAI, and more detailed information about how it will most likely be spread, as dead bird recovery mostly informs us of which species is susceptible, but not necessarily transmitting the virus.

Of human H5N1 cases, many are young adults or children between the ages of 10 and 29 years of age, leading some experts to hypothesize greater susceptibility in this younger age group [87]. However, most countries with human cases also have a median age of less than 30 years, the exceptions being China, Hong Kong SAR and Thailand with median ages of
In Cambodia the median age is the lowest among infected countries at 21 years of age. The age of H5N1 cases may not explain a greater biological susceptibility to H5N1, but it may instead reflect the portion of the population who has greater exposure to poultry in general. Alternatively, it may also represent some level of immunity in older populations.

It would be more beneficial to prevent H5N1 cases from occurring, than to respond to an existing outbreak since the obstacles such as illegal activities and resources to implement a response are nearly impossible to surmount, especially when long-standing agricultural practices are major risk factors for human exposure. A poultry vaccine program could be successful as a part of a prevention strategy more than a response to an established epidemic. However, prevention is a slower process, as can be demonstrated from the results of the education programs in Thailand, which still reports poultry and human H5N1 cases.

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