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Review

A one health perspective on HPAI H5N1 in the Greater Mekong sub-region

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ABSTRACT

Highly pathogenic avian influenza H5N1 has been a global concern for almost 10 years since its epidemic emergence in South-east Asia in 2003/2004. Despite large investment of resources into the region, the infection has not been eradicated and continues to result in outbreaks in poultry and a small number of human fatalities. This review synthesizes the knowledge base generated by a vast number of research activities conducted in the region and beyond, and adopts an interdisciplinary perspective consistent with the one health paradigm towards analysing the problem and formulating possible policy solutions. A key outcome of the work has been the need to integrate socio-economic and anthropological dimensions with any disease control and prevention activities traditionally informed by primarily epidemiological, virological and pathological attributes of the infection in poultry and wild waterbirds. Recommendations at a broad conceptual level are presented that acknowledge the diversity in the region with respect to livestock production, as well as the changing nature of the risk landscape as a consequence of the rapid economic development which some of the countries in the Greater Mekong sub-region are currently undergoing, as well as their strong trade links with China as the major economic power in East Asia.

Contents

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1. Introduction

Since its emergence, highly pathogenic avian influenza (HPAI) subtype H5N1 has attracted considerable public and media attention because the virus involved has been shown to be capable of producing fatal disease in humans. While there is fear that the virus may mutate into a strain capable of sustained human-to-human transmission, the greatest impact to date has been on the highly diverse poultry food systems in some affected countries. In response to this, HPAI H5N1 control measures have focused on implementing prevention and eradication measures in poultry populations, with more than 175 million birds culled in South-east Asia alone. The control methods used were based on classical approaches designed from a single discipline, i.e. a veterinary, perspective. They primarily involved culling, movement control and vaccination, which have proven to be effective for dealing with small to medium-size outbreaks of a relatively short duration. In the case of HPAI H5N1, it quickly became apparent that the infection cannot be eradicated from South-East Asia and China, and therefore classical control approaches will neither be effective nor sustainable. In order to improve local and global capacity for evidence-based decision making in the control of HPAI H5N1, inter- and intra-disciplinary approaches need to be adopted to develop cost-effective and efficient approaches for disease risk reduction. The current review examines the HPAI H5N1 epidemiology in the Greater Mekong sub-region (GMS), specifically the region represented by Cambodia, Lao People's Democratic Republic (PDR), Thailand and Viet Nam, and explores cross-disciplinary approaches to its control. A significant part of the evidence base considered here are the findings from an interdisciplinary project conducted by authors of this review.

2. Background on HPAI H5N1 in the Greater Mekong sub-region

2.1. Ecology/biology of avian influenza viruses

Avian influenza viruses (AIVs) have high mutation rates typical of RNA viruses (faulty transcription) resulting in relatively high rates of antigenic drift. In addition, due to their segmented genome (8 segments), genetic reassortment can occur in hosts that are infected by more than one AIV strain, facilitating host adaptation and resulting in high rates of genetic shift. AIVs therefore have a comparatively high evolutionary capacity to adapt to new hosts and changing environments [1,2].

AIVs representing nearly all 146 combinations of haemagglutinin (HA) (H1–H16) and neuraminidase (NA) (N1–N9) have been isolated from wild waterfowl where they cause asymptomatic infection and are considered to be endemic [3–5]. Generally, AIVs exhibit host specificity and are easily transmitted within the aquatic environment from one waterfowl species to another through the faecal–oral route. AIVs circulating in wild birds can spill over to domestic poultry, in which, initially, they are of low pathogenicity, causing mild respiratory disease. Non-waterfowl wild bird species appear to play a less important role for virus circulation, but can still fulfil a function as so-called bridge species that expose domestic poultry to infection [6–9]. In the 1990s, low pathogenicity AIVs (LPAIVs) have dramatically spread globally in domestic poultry, establishing chicken-adapted lineages. Several major outbreaks of avian influenza in domestic poultry due to H9N2 subtype occurred in the late 1990s in Germany, Italy, Ireland, South Africa, the USA, Korea, and China. While only few reports of HPAI in poultry are available for the 40-year period 1950–1990, 16 incidents of distinct HPAIV emergence have been recorded in the Americas, Australia, Europe, South Asia and South-east Asia since 1990. Severe epidemics have been associated with subtypes H5N2 in Mexico, H7N3 in Pakistan, H5N1 in China and beyond, H7N1 in Italy, H7N7 in Holland, and H7N3 in Canada, heavily burdening national animal health systems and causing massive losses to poultry industries [7,10,11]. HPAIV H5N1 emerged in South China in 1996, caused a major health scare in Hong Kong when the first human cases of infection and death were reported in 1998, continued to circulate and evolve in southern China for another 5 years, and expanded to other countries in South-east Asia in late 2003. In a second wave of expansion in 2005/2006, HPAIV H5N1 reached Central Asia, the Middle East, Europe, and Africa. Despite major efforts to control HPAIV H5N1, it is now firmly established in parts of China, Viet Nam, Cambodia, Indonesia, Bangladesh, India and Egypt [12]. Forty-four distinct HPAIV H5N1 genotypes have been identified between 1996 and 2006, with changes in dominant genotypes reflecting major reassortment events and establishment of distinct lineages in poultry in different geographical regions indicating separate foci of endemicity [13].

2.2. Poultry sector dynamics and consumer preferences

Poultry production in the GMS is heterogeneous in all its aspects, with the use of different species, different production and marketing systems, and supports a very diverse range of products and services. Typically, poultry are an integral feature of smallholder agriculture, where the majority of households keep a small (tens of birds) flock of 'indigenous', dual-purpose (meat and eggs) birds to meet household consumption needs, social obligations and minor cash expenses, the latter by sales through informal, live bird marketing channels [14–19]. This traditional, extensive poultry production system is virtually ubiquitous throughout the GMS. Comparisons produced by Rushton et al. [19] and by Otte et al. [17] based on various heterogeneous data sources in 2004–2005 suggest that extensive poultry producers (backyard subsistence and small commercial farmers) represent over 90% of farmers and poultry in Cambodia and Lao PDR, about 70–80% for both in Viet Nam. In Thailand, this group also represents the vast majority of producers, but only 10% of poultry. While the data sources for these figures vary in quality and are based on data from several years ago, the basic patterns are likely to be accurate. Simultaneously, intensive industrial poultry production systems, which follow the production model developed in industrialized countries, have been established particularly in Thailand where they produce 90% of poultry, but are still uncommon in the other GMS countries [17,19]. These two poultry production systems are extremes, between which 'hybrid' and/or intermediate, semi-intensive systems exist, including partial scavenging with feed supplementation, indigenous birds crossed with industrial poultry lines, partial reliance on 'formal' input supply systems, but operating at intermediate scales (hundreds of birds) and relying primarily on 'traditional', informal live bird marketing networks. Each production model has adaptive advantages and disadvantages and none is likely to disappear completely. The marketing channels for small scale producers are varied. Small scale producers sell birds through five different channels: aggregators, market vendors, households and other farmers, and restaurants. Aggregators are currently the most common buyers [16,17,20–24].

Free-grazing duck systems are a prominent feature in rice paddy areas in the GMS. Primarily intended for egg production, their farmers transport them intermittently or continuously to graze in rice fields. In southern Viet Nam, particularly in the Mekong river delta, this itinerant livestock practice is widespread [25]. Free-grazing duck flocks (up to several thousand ducks) can travel 10–20 km per day, moving across commune, provincial, and even national borders. For the owners of rice fields, ducks offer pest control and fertilization services, while for duck farmers, free-range grazing reduces the cost of feed by up to 50% [26]. Consequently, free-range grazing is an essential component of farmer livelihoods. These interactions are a highly productive utilization of resources for owners of both rice fields and ducks, but introduce serious animal and public health risks from an AIV perspective [16,22,27,28].

In Thailand, large-scale industrial poultry production is one of the economy's most important sources of animal-derived food, employment, and income. This intensive, industrial system is characterized by (a) being organized by stages of production with separate primary breeders, multipliers, and finishing producers (often contract farmers), (b) a small number of breeding companies dominating the global supply of genetic material, (c) specialization in meat or eggs and use of specific birds for each product, (d) use of high density feeds tailored to specific stages and lines of production, (e) increasing scales of production (thousands of birds) and (f) growing interconnectedness with the processing and agrifood marketing industries [23]. In Cambodia and Lao PDR, the 'formal', industrial poultry sector occupies a minor share in national poultry production (about 10% of poultry meat), while the situation in Viet Nam is intermediate between that of Thailand and Cambodia/Lao PDR (about a quarter of poultry meat) [18,21,22,29,30]. In each of these emerging economies, poultry production generally has grown faster than real incomes because the diet is shifting towards meat, but industrial production has been growing faster than other categories, driven by high levels of investment and restructuring of urban food supply chains. Although the market share of smallholder poultry production is shrinking, market-oriented smallholder producers still outnumber large-scale industrial production units [17].

Most grocery shopping occurs at traditional wet markets, although that is changing in urban centres, particularly in Thailand where supermarkets are taking on a major role [31–35]. Wet markets sell live and slaughtered whole fresh local chickens, while supermarkets sell frozen birds and fresh cuts of industrial chickens [36]. Live birds are cheaper than slaughtered ones and live chickens are preferred because customers can determine their quality and health. Across the region, consumers in markets with comparable access to local and industrial birds placed a premium of 30–100% on the former (per kilo of rendered meat) [22,23,37].

Consumers in different regions consistently rate safety as the most important attribute of poultry meat. However, while consumers are concerned about safety, they are limited in their ability to accurately evaluate the safety levels of the meat they purchase. Consumers that purchase live birds base safety considerations on the birds' movement and appearance while people that purchase slaughtered birds evaluate the meat colour and texture. It was very rare that anyone ranked price or taste higher than the safety of the product they buy [23]. Overall, the lack of knowledge of the farm source was the greatest reason for concern about safety, followed closely by disease risk and freshness considerations. Although many consumers prefer the taste of traditional poultry varieties, most urban Thai households primarily consume industrial breeds of chicken in part because they place a high premium on safety [23,37].

2.3. Household poultry keeping and marketing

Nearly all rural households in the GMS keep poultry for both sustenance and income, specializing in traditional bird varieties raised in low-input systems. Smallholders invest little to no resources in poultry production and sales of poultry account for only a small percentage of household cash incomes (less than 5%). Nonetheless, the minimal investment in production means that the percentage returns are extremely high and marketing poultry provides supplemental cash income to some of the poorest households in the region [17,23]. Because they are a millennial fixture of rural life in the GMS, poultry are deeply embedded in society and customs. Small flocks in and around households reduce pest damage, provide highly concentrated manure for direct application and composting, and offer surveillance against predatory animals and strangers. On a more personal level, poultry are popular as individual and family pets, and throughout this region they support an extensive, culturally important, and very lucrative cock fighting industry. The importance of this activity is reflected in the value of the most successful fighting cocks, which can sell for multiples of average annual household income. Finally, poultry are also integrated in many spiritual practices and festival events [38–40].

Market-oriented smallholder farmers source their inputs (eggs, day old chicks, some feed and supplements) from small commercial counterparts, and they are linked to downstream markets by individual aggregators and small poultry product vendors in local live bird markets (LBM) [20,23]. Aggregators reduce transactions and search cost for farmers, but act as monopsonists, reducing farmer bargaining power and their incentives to invest in product quality. Aggregators also blend bird stocks and obscure the origin of individual birds. The former activity can sharply increase infection risk, while the latter creates moral hazard and adverse selection that further undermine the incentive for farmers to invest in larger scale and product quality. For their part, LBM offer a variety of direct benefits to merchants and consumers, including freshness, discernable product variety and quality, and traditional food values that continue to elicit price premia in many GMS markets. Whatever the share of income from poultry, smallholder independent farmers exhibit negligible autonomous biosecurity adoption behaviour. They will often perceive the occurrence of disease in their animals as a periodic and natural event [41,42]. By contrast, most contract and large scale household producers have adopted some form of biosecurity measures in order to conform to contracts and/or protect investments undertaken. However, large(r)-scale producers could still benefit from increased access to technical knowledge and inputs. Both anecdotal evidence and direct observation around the GMS reveal extensive, diverse, and continuous transboundary trade in poultry products, despite the fact that such trade is either forbidden or much more strictly circumscribed. These flows, especially of live birds and eggs, through both kinship and commercial networks can extend from sources to destinations hundreds of kilometres from border crossings [12,43].

3. Epidemiology of HPAI in the Greater Mekong sub-region

3.1. Spatial and temporal patterns of HPAI H5N1 occurrence

In the initial epidemic waves, HPAI H5N1 risk in Thailand and Viet Nam was statistically associated with duck abundance, human population and rice cropping intensity but less strongly with chicken numbers [44]. In Viet Nam, the two main HPAI H5N1 risk clusters (Red and Mekong river deltas) not only coincide with irrigated rice areas in the lowlands, but also with areas of good market access and high poultry transaction frequency [45]. The latter suggests that the trade network, in which LBMs fulfil a key role, facilitates spread of the virus. A striking feature of the different epidemic waves in Thailand and Viet Nam is that they did not appear to be synchronous, which raises questions about the underlying factors that may define 'hot' periods during which increased virus circulation can be expected. In Viet Nam, the initial epidemics occurred before and during the Têt holiday period when demand for poultry and pork meat is particularly high, suggestive of poultry movements as important determinants of local epidemics [45]. In Cambodia and Lao PDR, HPAI H5N1 outbreaks occurred sporadically, and are probably associated with cross-border poultry trade: in the case of south-eastern Cambodia as spillover from southern Viet Nam and in Lao PDR as a result of poultry trade with southern China and northern Viet Nam. The small extent of the commercial poultry sectors in Cambodia and Lao PDR is a possible reason for the small size of the epidemics in these countries and endemicity is unlikely to develop due to the comparatively low density of poultry. Thailand experienced only a very small number of outbreaks between the major outbreak waves in 2004 and 2008. These outbreaks, caused by descendants of the original HPAIV H5N1 clades, suggested the existence of a local virus reservoir and are believed to have been associated with live poultry trade and cock fighting activities of farmers. In Viet Nam, since introduction of interventions (including large-scale vaccination campaigns in late 2005) outbreak incidence has been reduced significantly. There are still small-scale epidemics around the Têt holiday period, but also at other times of the year. The main foci of infection remain in the two large river deltas, particularly in the Mekong river delta [13,45]. Since 2008, HPAI H5N1 incidence in Viet Nam has been about 30–70 outbreaks per year involving single to multiple poultry flocks, up to 10 per year in Lao PDR and Cambodia, and none have been reported from Thailand (*data source*: FAO EMPRES-i). This represents a major achievement considering that in 2004 Thailand and Viet Nam had reported almost 2000 and 3000 outbreaks, respectively, which in 2005 dropped to about 200 and 2000, respectively. Myanmar reported 4 outbreak waves between 2006 and 2010 affecting different parts of the country, which based on clade types appeared to be epidemiologically connected with events in neighbouring GMS countries [13,46].

In the Red river delta, the predominant virus clades have changed over time while the original clade still dominates in the Mekong river delta [13]. This suggests different mechanisms of introduction and maintenance between the Red river delta and Mekong river delta. Northern Viet Nam seems to be subject to more frequent introductions of virus from southern China, whereas the Mekong river delta may have a local reservoir of circulating virus. Mechanisms for local maintenance of virus presence are unclear, but are particularly important in southern Viet Nam (and bordering areas of Cambodia) since introductions from outside the region seem to be less common [13]. Unvaccinated ducks have been implicated on various occasions as the cause of outbreaks in that region (*source*: HPAI H5N1 timeline document on www.who.int). The area within the Mekong river delta where the outbreaks occurred is known for a high duck density and large numbers of free-grazing ducks [13].

3.2. Risk of between flock transmission of HPAIV H5N1 and of transmission from poultry to humans

The likelihood of exposure of domestic poultry flocks to HPAIV H5N1 is influenced by production system characteristics and associated husbandry measures. The published data describing differences in infection risk between poultry production types needs to be interpreted cautiously, since it is likely to be affected by reporting bias and other factors compromising surveillance system sensitivity [45,47–49]. Still, it is possible to identify general epidemiological patterns on the basis of an assessment of the published information, as, for example, presented in some detail in Fournie et al. [12]. The systems within which poultry are kept in the GMS are complex. Most farming households will keep chickens, for subsistence and many for cock fighting, together with other agricultural production activities, such as rice production or aquaculture [50]. The chickens may be scavenging freely or be kept in small cage enclosures, hence very limited if any bio-exclusion or -containment measures are likely to be in place [12]. Transmission of HPAIV H5N1 can occur directly through contact between chickens from the same as well as neighbouring flocks, and given the large quantities of viruses excreted by clinically diseased chickens also indirectly by contamination of clothing or equipment [51]. Since there is a high likelihood of HPAIV H5N1 infected chickens developing obvious clinical signs and mortality, outbreaks will have significant adverse effects on farmers' livelihoods, and in the absence of vaccination are highly likely to be reported. The percentage of farmers keeping waterfowl will be high in areas with significant surface water area, such in river deltas or around lake areas, and can then be linked to aquaculture. These systems may be able to maintain HPAIV H5N1 without it being recognized, given that waterfowl are able to carry the virus without developing clinical disease [52–57]. Subsequent to the 2003–2005 outbreak waves in the GMS, industrialized poultry farms, primarily chicken farms in Thailand, have established bio-exclusion measures which have been effective at preventing introduction of infection, although it needs to be acknowledged that levels of infection in Thailand have been very low for several years and apparently zero since 2008. Considering these system features, it would seem that production systems involving waterfowl, such as in rice producing river delta areas, have the highest potential to maintain the virus locally, whereas the systems dominated by chickens produced for subsistence or small to medium scale commercial production are likely to require introduction from elsewhere, either through wild birds or through live poultry trade [58].

While wild birds in some instances might have been associated with the introduction of infection into the domestic poultry population, this source has several orders of magnitude lower importance for the spread and maintenance of HPAIV H5N1 infection, compared with human activities associated with domestic poultry. This conclusion is supported by the relatively clear trade association of the early outbreak waves in Viet Nam through their occurrence around the Tét holiday periods, and outbreak occurrence in northern Viet Nam along recognized trade routes (e.g. Dien Bien Phu and several other locations along the border between Viet Nam and China) [45]. Also, the risk pathway from release of live HPAIV H5N1 by wild birds through to exposure of domestic poultry that then has infection as a consequence is likely to be less effective, than any risk pathways associated with the poultry value chain.

The poultry trading network has an important role in the spatial spread of infection. The network involves farmers, poultry traders and consumers, with the traders linking between different farms when collecting birds as well as through unsold birds going back from an LBM to the home of the trader [24,59]. Data from Viet Nam indicate that LBMs host a highly dynamic population consisting of a mixture of domestic and occasionally wild bird species, representing a potentially large geographic area from which birds were sourced. Infected poultry will shed large amounts of virus, resulting in significant environmental contamination. It is therefore likely that within villages, through poultry traders collecting birds and at live bird markets there is a high risk of indirect transmission through contaminated humans or fomites. As mentioned above, infected waterfowl species can shed virus without necessarily progressing to a clinical disease stage, and therefore are likely to have a key role in the spread and maintenance of infection [60–62].

Live bird markets are a key feature of the epidemiology of HPAIV H5N1 in that they allow the mixing of birds from a large number of sources and of different species, including chickens and waterfowl [63–66]. Given the likely absence of hygiene at most LBMs, they thereby can be seen as large flocks that have a high turnover (daily) linked to a multitude of source and target populations, and may be able to maintain silent infection, without necessary occurrence of noticeable outbreaks [67]. This also increases the potential for antigenic drift as well as reassortment [13]. Fighting cocks are ubiquitous amongst the backyard and small scale commercial poultry producers in Thailand and other GMS countries, and result in additional mechanisms of potential spread of infection through movements to and from cock fighting events [58].

The intensity of transmission of HPAIV H5N1 during the 2004 epidemic in Thailand was quantified using a basic reproduction number R_0 between 2 and 5 [68]. A transmission model for the North of Viet Nam confirmed the Red river delta as a hotspot for sustained onward transmission [69]. This finding is consistent with spatial cluster analyses conducted for Viet Nam which identified clusters in the Red and Mekong river deltas [45].

The risk of HPAIV H5N1 transmission from poultry to humans is very low, as evidenced in the low morbidity, but case fatality rates are very high. Wang et al. [70] suggest that non-fatal human cases are likely to be severely underreported, and that therefore current case fatality estimates of over 50% are too high. Exposure risk is highest amongst producers as well as in LBMs [71,72]. Viet Nam has had the highest reported human cases and fatalities in the GMS with 59 deaths and 119 cases between 2003 and 2011. Second is Thailand with 25 cases and 17 fatalities, followed by 18 cases and 16 fatalities in Cambodia and 2 cases and 2 fatalities in Lao PDR (*source*: WHO – January 2012). It needs to be emphasized that in particular the case numbers are likely to be an underestimate due to underdiagnosis and underreporting.

Epidemiologic investigations of human HPAI H5N1 cases have shown that transmission of HPAIV H5N1 from poultry to humans is currently limited to individuals who may have been in contact with the highest potential concentrations of virus shed by poultry [71]. This suggests that there may be a minimum level of virus concentration needed for effective transmission to occur and that circulating HPAIV H5N1 strains have not yet mutated to transmit easily from poultry to human, and clearly not from human to human. The mode of transmission varies within and between countries ranging from exposure to poultry or poultry products during a visit to a LBM to preparing infected poultry or swimming or bathing in ponds, which are frequented by poultry [71–73].

It has to be concluded that infection of humans with HPAIV H5N1 currently is fairly unlikely, even in the absence of specific hygienic prevention measures. Nevertheless, any human case of infection apart from the high case fatality rate, represents potential for virus reassortment that could produce a virus variant that is transmissible between humans [71,74].

4. HPAI H5N1 risk management and its impact

4.1. Driving forces of national HPAI H5N1 risk management policy

Thailand is one of the world's largest poultry meat exporters (*source*: FAOSTAT). Therefore, the risk management response of the Thai government to the emergence of HPAI H5N1 in 2003/2004, and in particular the major epidemic in 2004 was very much influenced by the highly integrated intensive poultry producer stakeholder group as well as by the extensive publicity around the relatively small number of human fatalities [18]. It was considered crucial to achieve status of disease freedom as soon as possible, and therefore during the 2004 epidemic a control policy of large-scale culling without vaccination was adopted [18]. The risk management since then has been aimed at minimizing the likelihood of reoccurrence, and key components have been the introduction of intensive nationwide surveillance and of a compartmentalisation scheme for commercial poultry farms. The influence of backyard and small-scale chicken as well as duck farmers appears to have been much less significant, as has been that of cockfighting enthusiasts which represent a large part of rural communities [18].

In Viet Nam, policy development at national level is driven by state actors, i.e. the Vietnamese Communist party with a weak link to other sections of society, particularly with farmers who represent 70% of the population [30]. Furthermore, the effectiveness of policy implementation at central government level is compromised by the relative independence of local authorities [30]. This situation results in different control policies between provinces or districts, such as for example different levels of compensation between provinces [75]. Significant introductions of foreign aid also had a strong influence on policy development [30]. While the occurrence of HPAI H5N1 had not been acknowledged by the Vietnamese authorities until the beginning of 2004, from then on its control was given high priority, such that between 2005 and 2006 the Vietnamese government spent US $266 million on avian influenza control [18]. The occurrence of the epidemic with at the time the highest number of reported human fatalities and the associated media reaction also resulted in rural and primitive farming practices being blamed for it [39,75]. The key difference in the control strategy compared with Thailand was the use of large-scale vaccination. In Vietnam, 65% of poultry producers were smallholder free-range systems which contributed 60–70% of all chickens sold per year. Industrial farming systems produced 18–20% of chickens, but only represented 0.1% of all poultry farms [16]. Vietnam does not have significant live poultry and associated products exports. As a consequence of this poultry production system structure, the industry stakeholders had relatively little influence on the policy response [30,76].

Both, Lao PDR and Cambodia only reported a very small number of outbreaks during the major epidemics in 2004/2005 within the GMS. They have low poultry density, and their policy response was strongly influenced by foreign aid and influence, largely due to poor animal and human health infrastructures [14,29].

4.2. National control measures and their efficacy

All GMS countries considered in this review engaged in promoting improved biosecurity at farm level as a method for preventing introduction of infection to poultry flocks. The specific approaches were broadly consistent with recommendations made by international organizations [77]. But as discussed by Cristalli and Capua [78], the incentives for promotion or adoption varied significantly between countries, with Thailand having achieved the highest level of awareness, and Cambodia and Lao PDR the lowest.

In Thailand, measures adopted for disease containment adhered closely to provisions laid out by FAO, WHO and OIE. These included a comprehensive cull of all susceptible poultry from farms located within a 5-km radius. Compensation was among the highest paid in South-east-Asia. Movement restrictions were imposed within a 50-km radius of outbreak locations. A 90-day ban imposed on export of poultry from affected areas, redundant to prohibitions from other countries [47]. From mid-2004, due to the reduction in outbreaks achieved by the disease containment policy, it was possible to focus on large-scale active surveillance involving diagnostic assessment of very large numbers of samples collected from farms, as well as in relation to movements and slaughter. Any outbreaks were controlled using culling within zones of only 1-km radius. Information campaigns were implemented in relation to human health protection and poultry biosecurity [18,79]. To specifically protect industrial poultry farms from infection through exposure to potential presence of infection in backyard and small-scale commercial production systems, a government-funded scheme was implemented that involved establishment of disease-free compartments surrounding some industrial poultry farms. The biosecurity protocol involves intensive surveillance for infection in a 2-km buffer zone around the compartmentalized farms, as well as other measures [79,80].

Viet Nam implemented a wide range of control measures, including large-scale culling, movement controls and closure of live poultry markets, banning poultry keeping in some major cities, campaigns to educate the public about preventive measures. The culling policy was revised after the first epidemic wave (44 million birds culled) as it became clear that extensive culling based on pre-established geographic criteria (i.e. 1-km radius ring culling) was too expensive and hard to perform given that farmers were not willing to give up apparently healthy birds [30]. In addition to the direct cost of culling, farmers demanded compensation, which represented a major fiscal burden. In subsequent waves, targeted culling of high-risk bird populations immediately adjacent to infected farms was employed, dramatically reducing the number of birds culled. From 2005 onwards, Viet Nam launched comprehensive, nationwide vaccination campaigns for all birds, to a large extent funded by donors [30]. Vaccination coverage achieved by the mass vaccination campaigns was at best moderate [69]. Although the within-flock basic reproduction number of infection (*R*0) has been significantly reduced in the fourth epidemic wave (vaccination-based control policy) when compared to the second epidemic wave (depopulation-based control policy), the mean within-flock *R*0 of the fourth epidemic wave was still not significantly below unity, suggesting problems with obtaining the required vaccination coverage within some flocks [81,82].

Cambodia's control policy involves poultry movement restrictions and permitted culling of infected flocks without compensation. Also, 3-km protection zones and 10-km surveillance zones were established around outbreaks [15,29]. Temporary suspension of sales and purchases of birds was mandated. However, law enforcement is weak and compliance is low [15,29].

Experience from Viet Nam (and also China) has shown that large-scale vaccination does not eliminate infection [13,81,83,84]. Overall, control measures in place during the 2007 wave of outbreaks in Viet Nam reduced the number of communes capable of spreading infection by an estimated 11%. This was achieved at a far lower social and economic cost than during previous waves. However these gains have to be balanced against the cost of maintaining levels of effective vaccination protection in an endemic situation [83]. As estimates suggest that the infectious period at population level has increased following vaccination, the impact of waning levels of immunity as the initial impetus to vaccinate is lost, coupled with the effects these changes may have upon the ability to detect outbreaks, remains an issue which needs to be addressed [69]. On the other hand, a control strategy without vaccination involving a combination of activities including intensive surveillance such as practiced in Thailand around compartmentalized poultry production units appears to be able to eliminate infection, and apparently prevent outbreaks of disease [13].

An important aspect of effective prevention of spread in the event of outbreaks is their early detection, as has been demonstrated by mathematical models [69]. The most cost-effective mechanism for achieving this goal will be to incentivise farmers to report any suspect cases and for the animal health authorities to be able to react quickly. A generic set of guidelines for on-farm biosecurity has been published by the Food and Agriculture Organization of the United Nations (FAO), and local stakeholders will implement adaptations of these which are relevant in their specific context [36,77]. It is important to recognize that biosecurity does not come in 'black or white' but in shades of grey. It is incremental, i.e. one measure can be put on top of another, and sensibly should address the biggest risk(s) first. This, however, means that biosecurity is to a large extent context-specific and, although in qualitative terms it is known how HPAIV H5N1 may spread, there is only limited quantitative data on the relative importance of different pathways of infection in different production systems. As all investments, investing in biosecurity is subject to the law of diminishing returns and it is neither economically efficient, nor biologically feasible, to reach 100% biosecurity. For privately funded investment in biosecurity the benefit to the individual needs to at least cover the cost over the lifetime of the investment. Given that investing in biosecurity has a fixed cost component, cost per bird protected will be lower for larger production units than for smaller production units, hence economic incentives differ by scale of production (in addition to the fact that larger flocks may have more transactions and therefore often more risky contacts than small flocks). Consequently, smallholder behaviour of limited investment into biosecurity is economically rational. Therefore, approaches to disease control need to be congruent with local social, cultural, economic and political realities [41,42]. Policies aimed at behaviour change which should be to HPAI H5N1 control, need to build on an understanding of existing behaviour, as the latter is likely to have very solid foundations, otherwise they are likely to fail. Biosecurity 'kills several birds with one stone' and returns at the beginning of the 'biosecurity function' are high. If context-specific (i.e. proven to work and not requiring radical changes in a given environment and production system), the introduction/improvement of biosecurity is potentially pro-poor rather than anti-poor, provided producers have access to the required capital and knowledge, and are given sufficient time and support to adapt.

4.3. Livelihoods and economic impacts of HPAI H5N1 disease and control

HPAI H5N1 affects animal production via three main pathways. Firstly, it causes direct losses to producers and other actors connected to the production and marketing of poultry through morbidity and mortality and the private costs associated with *ex ante* risk mitigation or *ex post* coping measures and the need to reinvest in replacement birds. Second, HPAI H5N1 has severe impacts through government intervention, which carries a cost borne by the public at large and affects producers and associated up- and downstream actors. Thirdly, HPAI H5N1 impacts arise through demand shocks created by consumer fears of contracting the disease. In concert, these impacts can lead to irreversible industry readjustments.

On a national scale, direct poultry losses from HPAI H5N1 disease and related culling were minor in Cambodia and Lao PDR, while both in Thailand and Viet Nam some 60 million birds were culled during the initial waves in 2004, which at the time represented between 20 and 30% of the standing poultry population [17,85]. Compensation payments and other public mitigation measures implemented by the respective governments transferred some of the financial burden from the private to the public sector [86]. Apart from direct losses, movement restrictions, marketing bans and consumer reluctance to purchase poultry and poultry products led to a severe drop in activity throughout the entire market-oriented sector of the poultry industry in the GMS, affecting feed producers, traders, processors and retailers (not eligible for compensation). The economic downturn of the poultry sector was partially compensated by increasing activity and prices in sectors producing substitute food products [17,37].

The industrial/corporate poultry sector has adapted to HPAI H5N1 by exerting increasing control over every stage of production and raising sanitary standards [17,87,88]. The high costs required to build the necessary infrastructure and difficulty of securing loans without collateral, make it unlikely that low-income households would be able to enter into any stage of industrial poultry production. Even farmers that presently have contracts may have difficulty adapting to the highly competitive conditions if they are required to make expensive upgrades to farm infrastructure. The high fixed costs of processing, controlled primarily by the integrators, pose another barrier prohibiting entry of independent farms into the system. Additionally, in Thailand, because of export orientation, processing plays an increasingly important role in the organization of poultry production [17,23]. Collectively, small-scale subsistence-oriented poultry keepers suffered the largest cumulative economic losses from HPAI H5N1 disease and control in the GMS while the disease posed the highest livelihoods threat to market-oriented poultry producers and market agents (in their majority usually relatively small-scale enterprises) specialized in poultry. The reason for this discrepancy is that the latter only represent a minority of producers, but a minority whose livelihoods are most affected by longer lasting HPAI H5N1 outbreaks and/or protracted control measures due to their relatively high investments and specialization in poultry [17].

4.4. Alternative approaches to HPAI H5N1 control

Animal diseases are part and parcel of farmers' everyday experience and local responses are determined at least as much by local cultural as by imposed technical rationales. There is a direct link between the perceived value of poultry and the optimum disease management approach from an individual farmer's perspective. Higher valuation of live poultry will increase the care taken, possibly enhancing monitoring efforts and thereby reducing the culling radius. Enhancing the value of poultry, via improved marketing and safety, would ultimately result in less drastic HPAI H5N1 control policies. Numerically, small farmers and enterprises dominate the market populations across GMS agrifood systems. These networks confer livelihoods on such low income agents only because the costs of participation are very low. If control measures impose significant additional costs on the operations of any category of participation in these markets, they will be forced out quickly [37]. Moreover, because of low savings and the need to re-commit to some other livelihood activity, displacement like this can be irreversible. By promoting risk sharing supply chain relationships, such as contracting, certification, and traceability, individual agents can contribute to a local commons of lower disease risk, more credible product quality, and higher value added across low income networks extending from farmers to consumer households. In these circumstances, every value chain participant has a shared interest in more diligent safety production, distribution, and marketing practices. Such virtuous cycles of value creation/sharing can overcome endemic problems of moral hazard and adverse selection [22,23]. Based on a simple statistical value of life calculation, the gain from reduced pandemic risk is in the billions of dollars, annually [89]. The private sector is unlikely to invest optimally in development of improved surveillance and risk reduction measures. Therefore, development of disease surveillance technologies has a global public good element, and their development should be supported by public sources. To deal with distributional issues within and across countries and regions, a regime of penalties should be accompanied by fixed transfers, including from third countries which benefit from reduced disease risk.

5. Conclusions

The HPAI H5N1 situation in the GMS countries illustrates the importance for adopting an interdisciplinary (or one health) approach towards risk assessment and management when dealing with disease problems. The countries are diverse across all aspects relevant to animal disease control, including the role of agriculture in the overall economy, livestock sector and market structure, individual and societal risk perceptions related to livelihoods and public health, national and local governance systems. This diversity limits the generality of national solutions and poses a challenge to multilateral coordination. Standard disease response prescriptions that populate international guidelines and are replicated in country plans assume well-functioning human and animal health systems, rapid and efficient response capacity, and up-to-date epidemiological information and technical expertise, none of which prevail in most GMS countries. Technocratic, expert-driven, top-down solutions falter in the face of bureaucratic and political complexity, institutional weakness, and local market imperfections.

Diseases can be controlled and even eradicated without having to reduce transmission risk to ZERO. To be cost effective, control measures should first be applied to the highest risk groups/areas/activities and proceed down the risk hierarchy as resources allow and aggregate risk necessitates. Disease control authorities need to recognize that the risk of livestock disease is a combined result of biological processes and economic as well as social behaviour extending across the entire agrifood sector, including livestock keepers, their input suppliers, their downstream market partners, and of agents within the animal and public health system itself. 'Conventional' disease control strategies, emphasizing public surveillance and economic sanctions, present significant long-term fiscal obligations and adverse incentive problems.

In the short term it will be impossible to eradicate HPAI H5N1 infection from the region. It is entirely feasible, however, to reduce rates of transmission to a degree that forestalls development of local reservoirs of infection and detects incursions before they have spread 'out of control'. Targeted control measures, such as reducing infection risks at LBMs, as well as prevention measures aimed at domestic duck production, would make important contributions to this 'second-best' objective. Transboundary HPAI H5N1 transmission risk within the GMS appears to be high and Thailand, Lao PDR, and Viet Nam are exposed to HPAIV introductions from southern China. In this setting, national and international resources for domestic eradication will not achieve their objectives, suggesting an urgent need for more determined multilateral policy coordination [13].

Poultry are rarely the primary source of income for rural households, and within the household level or small scale poultry 'enterprise', HPAI H5N1 is not normally the disease of primary concern. If this disease is seen as exceptional by other stakeholders, emergency responses need to communicate this with meaningful development responses that reward smallholders for internalizing national or global health risks. Unfortunately, these two 'response modalities' are decoupled both at international and national levels.

In the context of emergency response, risk management of HPAI H5N1 has not been integrated with other poultry or livestock disease issues, even though these may matter more to the smallholders. Support for producer 'diversification' and quality improvements appear a more promising tool for HPAI H5N1 risk reduction than targeted compensation for stock losses. The same reasoning applies to production and trade bans, which cannot be enforced and may make matters worse.

HPAIV H5N1 now appears to be endemic in parts of the GMS and domestic and (especially) external public resources for control measures will be difficult to sustain at previous levels [13]. Attempting to improve the biosecurity of millions of backyard producers is an ineffective use of scarce resources, especially through public funds in countries with many high development priorities. Publicly funded, routine large-scale vaccination campaigns are costly and appear to be inefficient [90]. Targeted vaccination of specific high-risk groups can achieve comparable risk reduction at a fraction of the cost [83]. For within-country areas with apparent endemic infection (e.g. Mekong delta in Viet Nam), eradication programmes should be considered, but carefully targeted at the mechanisms responsible for maintenance of infection. Hygiene and diagnostic effectiveness needs to be improved in LBMs and associated value chains. These include poultry trade networks (e.g. allow movement in one direction – downstream; limit distance travelled), live bird markets (rest days, species segregation) and targeted duck surveillance, including accreditation of infection-free duck farms. Establishment of infection-free zones or compartments is possible, as has been demonstrated by Thailand, and can be used as 'success stories' and technology incubators. Economic outcomes for these groups may also induce emulation/adoption elsewhere. Cross-border trade, particularly with southern China, is an important mechanism for recurrent introduction of infection to the GMS region. This risk needs to be managed, or national eradication programmes will be futile. Simple prohibitions of cross-border trade are ineffective and create informal flows that make infection processes unobservable. The only practical solution is multilateral coordination to effectively monitor flows of animals, products, and infrastructure. Reducing virus prevalence in poultry will significantly reduce the risk of humans to become infected, and this can be further reduced by public education campaigns limiting high risk behaviour.

Conflicts of interest

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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