Published in final edited form as:
Spat Spatiotemporal Epidemiol. 2012 September ; 3(3): 173–183. doi:10.1016/j.sste.2012.01.002.

Risk factor modelling of the spatio-temporal patterns of highly pathogenic avian influenza (HPAIV) H5N1: a review

Marius Gilbert[1,2] and **Dirk U. Pfeiffer**[3]

[1]Biological Control and Spatial Ecology, Université Libre de Bruxelles, av FD Roosevelt 50, B-1050 Brussels, Belgium

[2]Fonds National de la Recherche Scientifique, rue d'Egmont 5, B-1000 Brussels, Belgium

[3]Veterinary Epidemiology & Public Health Group, Department of Veterinary Clinical Sciences, The Royal Veterinary College, University of London, United Kingdom

Abstract

Highly pathogenic avian influenza virus (HPAIV) H5N1 continues to impact on smallholder livelihoods, to constrain development of the poultry production sector, and to cause occasional human fatalities. HPAI H5N1 outbreaks have occurred in a variety of ecological systems with economic, agricultural and environmental differences. This review aimed to identify common risk factors amongst spatial modelling studies conducted in these different agro-ecological systems, and to identify gaps in our understanding of the disease's spatial epidemiology. Three types of variables with similar statistical association with HPAI H5N1 presence across studies and regions were identified: domestic waterfowl, several anthropogenic variables (human population density, distance to roads) and indicators of water presence. Variables on socio-economic conditions, poultry trade, wild bird distribution and movements were comparatively rarely considered. Few studies have analysed the HPAI H5N1 distribution in countries such as Egypt and Indonesia, where HPAIV H5N1 continues to circulate extensively.

Keywords

Spatial epidemiology; avian influenza; H5N1

Introduction

Highly pathogenic avian influenza virus (HPAIV) type H5N1 causes a highly contagious disease of poultry that was first observed in the province of Guangdong, China, in 1996 (1). For several years, it was only recorded in China and Hong Kong where it resulted in human morbidity and fatality (2). During late 2003 and 2004, the virus spread extensively and caused new outbreaks in China, but also in several other Asian countries including Vietnam, Thailand, Lao, Cambodia, Indonesia, Japan and South Korea. In summer 2005, it spread westwards and outbreaks were reported from Kazakhstan and Russia. This was soon

---

Corresponding author: Dr Marius Gilbert, Biological Control and Spatial Ecology CP160/12, Université Libre de Bruxelles, av FD Roosevelt 50, B-1050 Brussels, Belgium, Tel +32 2 650 37 80, Fax: +32 2 650 24 45, mgilbert@ulb.ac.be.

followed in autumn 2005 and winter 2005/2006 by outbreaks reported in many European countries, and in several African countries. All together, and over the entire period 2003–2011, the virus was reported in over 60 countries distributed across Asia, Europe and Africa (3,4). In many countries where it was introduced, HPAIV H5N1 only persisted for a few months, and was soon eradicated. However, to date it persists endemically or shows occasional resurgence in a limited number of countries including Bangladesh, Cambodia, China, Egypt, India, Indonesia, Japan, South Korea, Russia, Vietnam (3,4).

Considering its geographical distribution, its socio-economic impact on poultry farming and smallholder livelihoods, and the mortality caused in the wild avifauna in some particularly spectacular outbreaks, the HPAI H5N1 panzootic has no known precedent. HPAIV H5N1 has hence been subject to considerable fundamental and applied research aimed at studying the disease from the perspective of many disciplines. The number of published studies on HPAIV H5N1 ranged between 23 and 56 publications per year prior to the panzootic. It increased to 1098 publications in 2010 (see Fig. 1, ISI Web of science search 19th September 2011 on "H5N1" term). This is, however very modest, compared with, for example, "climate change", that generated > 25,000 papers in 2010).

A fraction of this abundant literature has focused on the epidemiology of HPAIV H5N1, and more specifically on the factors associated with its presence in various regions and countries. Various approaches have been used, including qualitative and descriptive studies investigating the conditions of HPAIV H5N1 introduction and spread, empirical studies based on HPAI H5N1 distribution data, and more theoretical work focusing on the exploration of disease control scenarios.

This literature review focuses on studies that have studied explicitly the spatial distribution of HPAI H5N1 based on empirical data. These studies that fall under the general definition of *spatial epidemiology* (5,6) have analysed disease distribution data with the aim to characterize their spatial or temporal pattern (e.g. clustering of cases), to identify spatial predictors associated with disease presence, and in some instances to map disease risk over large geographical areas. Case-control studies carried out at the farm or market level were also included in this review, provided that some spatial variables (e.g. distance to road, local human population density) were considered as potential risk factors.

The objective of this review was twofold. First, given the variation in ecological systems in which HPAI H5N1 cases have occurred, it would be useful to compare risk factor patterns. Any consistencies in such patterns would strengthen associated causal interpretations and potentially lead to improved control or prevention policies. Conversely, factors found significant in some circumstances and not in others, may reflect differences in transmission patterns between countries, but may also be indicative of spurious statistical relationships. Second, synthesizing the knowledge generated by spatial epidemiological studies on HPAI H5N1 also aimed at identifying any gaps in relation to risk factors, countries, or epidemiological conditions, and towards which future research could be directed.

Materials and methods

We searched the ISI Web of Science (1996- end 2010) and CAB abstracts (1996 » - end 2010) with the terms « avian influenza » combined with the terms « Spatial », « Risk », « Cluster », « Map » or « Distribution ». The search was conducted on April, 16th 2010, and updated on August, 9th 2011. Based on these results, we performed a first selection including all papers with explicit reference to spatial data on avian influenza. The reference list of these papers was then carefully checked to identify other papers that had not been identified through the initial searches. These references were then grouped into six categories: i) papers where the main focus was the statistical analysis of disease distribution data; ii) papers that analysed or discussed HPAI H5N1 risk, but from the perspective of wild birds: this includes papers that have attempted to predict the risk of HPAIV H5N1 introduction through wild migratory birds, and papers that have primarily analysed wild bird migration data but in relation to the location of HPAI H5N1 outbreaks: iii) papers that analysed HPAI H5N1 risk in relation to poultry trade: this includes risk assessments of introduction by trade, or trade network analysis in the context of HPAIV H5N1 prevention strategies; iv) papers using mathematical modelling to quantify transmission parameters, or to test disease control scenarios; v) phylogenetic studies with a strong emphasis on the spatial dimension, and vi) review papers.

Only papers from the first category, i.e. focussing primarily on the statistical analysis of HPAI H5N1 disease and infection data, were included in this review, and we restricted our selection to papers on disease and infection caused by HPAIV subtype H5N1. These studies were classified based on several criteria: the study area, the unit of analysis, the analysis methods, the type of factors considered, grouped into 9 categories: i) farming practice and local biosecurity, ii) poultry and livestock census data, iii) anthropogenic variables, iv) socio-economic variables, v) variables indicative of the presence or abundance of wild birds, vi) variables indicative of the presence or abundance of rivers/, lakes or wetlands, vii) eco-climatic variables obtained using weather station data or remote sensing, viii) land-use and cropping variables, and finally ix) topography. For each of the factors identified as significant in the different studies, we noted the significance ($p < 0.05$; $p < 0.01$; $p < 0.001$) and signs of the association with HPAI H5N1 presence in the case-control and cross-sectional studies. When a factor was tested in both a uni- and multi-variate model, the significance and sign of the factor in the multivariate model was used.

Results

The first selection resulted in 115 references relevant to avian influenza and spatial epidemiology in their widest sense. Of these, 55 reported results of empirical studies on AI distribution, 29 papers pertained primarily to wild bird migration patterns in relation to AI risk, 8 papers focussed on AI risk assessment based on poultry trade patterns, 12 papers had a primary focus on mathematical modelling, 6 papers were phylogenetic studies with a strong spatial dimension, and 5 were review papers. Out of the 55 papers based on empirical AI data, 47 papers pertained to HPAIV subtype H5N1.

These 47 can be grouped into four main study categories. First, descriptive studies ($n = 9$) that included descriptive statistics on HPAI H5N1 distribution data without explicit statistical hypothesis testing (e.g. maps of cases, epidemic curves), with discussion of spatial and/or temporal patterns. Second, spatio-temporal pattern studies ($n = 10$) where the spatial and/or temporal distribution of HPAI H5N1 cases was studied using statistical hypothesis testing in order to characterise their space and/or time clustering. Third, case-control studies with farms, markets or even wetlands as unit of analysis ($n = 5$) and where HPAI H5N1 cases were contrasted with a selection of controls using a multivariate analysis of a set of risk factors (and where those factors included one or more spatial variables). Finally, cross-sectional studies ($n = 23$) that analysed the the statistical association between the presence of HPAI H5N1 disease or infection and various risk factors over an entire study area. These latter studies also aimed to predict the spatial distribution of HPAI H5N1 risk.

The geographical extent, spatial resolution, and unit of analysis and methods of those 47 studies are detailed in Table 1. The majority of studies was carried out using the extent of a whole country ($n = 25$) or a set of countries ($n = 14$), with much fewer studies covering a sub-national ($n = 6$) or global ($n = 2$) extent. In most studies, the unit of analysis was an outbreak (=case), based on somewhat varying definitions. In this respect, cases were based on laboratory sample testing of HPAIV H5N1 presence at best, or based on the presence of abnormally high mortality in poultry flocks without laboratory confirmation at worst. In addition, in all studies except those based on Thailand data (7–9), and the analysis of virology sampling resulting from active surveys in China (10) detection was based on passive surveillance that can be affected by varying levels of underreporting bias. Depending on the study and original data source, the case may represent epidemiological units of different type and size: farms, markets, villages, administrative units, or an entire 1 km or 4 km geographical raster cell. However, a common feature of the all studies was that the case was geo-referenced using point location GPS coordinates or by the name of the administrative area unit where HPAI H5N1 had been identified at a particular time. When based on an administrative area unit, for the purpose of analysis, HPAI H5N1 occurrence data were converted into point location coordinates using the polygon area centroid. One of the difficulties noted in studies using data aggregated across several countries was the inconsistency in case definition, and the lack of information on the accuracy of the geographical location. For example, the point coordinate locations may at best represent the GPS coordinates of a farm or village where HPAI H5N1 was confirmed by a laboratory test, and at worst be the centroid of a relatively large geographical area such as a province or district, and its position may therefore be quite distant from the actual location of the outbreak.

In terms of overall coverage, only a limited number of countries that reported HPAI H5N1 cases has been subject to dedicated studies, including: Bangladesh, China, Indonesia, Nigeria, Romania, Thailand and Vietnam. It is noticable that the spatial distribution of HPAI H5N1 cases has not yet been studied in Egypt, where the second highest number of human cases has been observed. Similarly, no dedicated studies have been carried out to date in South Korea, Japan or Cambodia where the disease shows occasional resurgence.

It is difficult to produce a meaningful summary of the results generated by descriptive studies, because they tend to be highly location-specific. Studies focussing on the detection of spatial, and/or spatio-temporal patterns of cases all have identified clusters relevant to the particular local context, and they differed in the method used to characterise the pattern (K-functions, geostatistics, customised transmission model) as well as in the geographical extent and interpretation of the identified clusters.

Case-control and cross-sectional studies are easier to compare because most papers used comparable statistical approaches, although they differed in their unit of analysis, case definition, spatial extent, and/or selection of risk factors (Table 1). As illustrated in Table 1, 21 out of the 28 studies analysing the distribution of HPAI H5N1 disease or infection in relation to risk factors used methods based on the multivariate logistic regression framework (Table 1), with, alternative approaches such as boosted regression trees (10) and ecological niche modelling (11–13) only rarely being used.

Table 2 summarizes the risk factor categories that were considered in case-control and cross-sectional studies. The most commonly represented risk factors are poultry & livestock variables, anthropogenic variables (human population density, distance to roads & cities), and variables describing the environment in terms of water and land use. Eco-climatic and topographic variables were also used in a number of studies, but to a lesser extent. Variables describing local conditions of farming or marketing were for understandable reasons limited to sub-national case-control studies. The small number of studies integrating socio-economic variables, trade data, or variables describing wild bird populations is more surprising, especially if one considers how much these factors could potentially influence HPAIV H5N1 introduction and spread.

The individual risk factors that have been found to be significantly associated with HPAI H5N1 risk (positively or negatively) in case-control and cross-sectional studies, and the direction and statistical significance of their relationship with the presence of HPAI H5N1 are summarized in Table 3, grouped by risk factor category.

Factors describing farming, hygiene and bio-security conditions are diverse, and differed between studies (Table 3). However, when significant, those factors on enhanced biosecurity and hygiene practices were found to be associated with a reduction of risk (e.g. clear zoning in live-bird markets, daily solid waste disposal in markets, use of disinfectant to clean poultry areas, or raising ducks and chickens in different shelters). Conversely, factors associated with increased movements of farmers, workers or middlemen from and to the farm (purchase of live poultry from another farm, receive visitors on premises, workers live outside premises), or factors reflecting possible transmission through slaughtered animals bird slaughtering in live bird markets, feeding with slaughter remnants of purchased chickens, presence of slaughterhouse in sub-district) were found to be positively associated with HPAI H5N1 risk. Paul et al. (14) identified a negative association between HPAI H5N1 risk and the daily time spent attending to a farmer's fighting cocks, which may be a reflection of increased attention to poultry living conditions in general.

Most studies included poultry variables as a risk factor (Table 2),although their categories differed. The factor found to be most frequently associated with HPAI H5N1 presence was the density of ducks, free-grazing ducks or domestic waterfowls, and a positive association was reported repeatedly in different studies in Southeast Asia, East China and South Asia. In contrast, the sign of the statistical relationship between chicken density and HPAI H5N1 presence differed across studies and countries. This could have been influenced by the diverse ways in which chicken density has been represented in terms of categorisation, production system and sub-species representation. For example, several studies made a distinction in terms of production systems. The density of native chickens was used as a proxy for backyard production (14,7,9,8), and the density of poultry flocks (15), the number of commercial chickens (16), or broilers and layers density (17) were used as proxies for different commercial production system. In contrast, other studies such as Yupiana et al. (18) did not make any distinction of poultry, and used an aggregated poultry density variable that does not differentiate production systems, or chickens and ducks. As a consequence, the respective effect of these different types of poultry cannot be separated. A few other poultry variables were also analysed, such as for example the density of cocks that was found to be positively associated with HPAI H5N1 risk in Thailand by three different studies (one should note that all three studies are based on the same dataset).

A positive association was found across several countries and regions between HPAI H5N1 presence and different variables relating to human population. These include a positive association with human population density (or agricultural, rural, or urban population density) and with the density or presence of roads, and a negative association with the distance to the nearest city or highway. In addition, two studies considered socio-economic variables, and found a negative association between HPAI H5N1 risk and the % of households with electricity on one hand (15), and with the purchasing power per capita on the other hand (19).

Although several studies considered or mentioned wild bird data in their analyses, this was done in relation to large-scale patterns of migration, and not included as an explicit risk factor with the exception of only one study that found a statistically significant association between HPAI H5N1 risk and the presence of contacts with pigeons at the farm level (20).

Water-related variables were also positively associated with HPAI H5N1 risk in the studies that included them, and this was expressed through a positive association with access to water in Bangladesh (20), the presence of a river stream or flooded land area in Romania (21), the proportion of land occupied by water in China (10), or the presence of a pond or canal near the farmhouse in Thailand (14). A similar relationship was also expressed as a negative association with the minimum distance to lakes, rivers or wetland in China (22). Only one study found a different type of relationship, with HPAI H5N1 found to be negatively associated with the proportion of land occupied by water in Indonesia (18). The study by Iglesias et al. (23) was somewhat different, because the unit of analysis was the wetland itself.

Relationships between HPAI H5N1 presence and eco-climatic variables are difficult to summarize because many different variables were considered in the analyses (temperature, precipitation and NDVI), with different aggregation periods (monthly vs. yearly values). Furthermore, studies that have employed eco-climatic variables used ecological niche modelling that does not provide an overall significance or direction of effect for a particular variable, and the comparison of their results with other studies is hence more difficult.

Finally, the paper by Si et al. (24) that considers several of such factors focussed on the presence of HPAI H5N1 in wild birds, and merely defined their habitat.

Land use variables were studied in a limited number of papers on Thailand, Vietnam and Indonesia (a study on Europe only used wetlands as unit of analysis) and revealed a positive statistical association between HPAI H5N1 risk and cropping intensity, the proportion of land occupied by rice, and the proportion of land used for aquaculture. Henning et al. (15) also found a negative relationship with sweet potato yield.

Finally, the association between HPAI H5N1 risk and elevation was analysed in several studies and was found to be negative, i.e. indicating higher risk in low elevation areas.

Discussion

Considered all together, three main types of factors were found to be positively associated with HPAI H5N1 risk across studies and regions: the density of domestic waterfowl, anthropogenic variables (human population density, proximity to roads or cities) and variables indicative of the presence, proximity or abundance of water (abundance of water or proximity to water). The causal link that these relationships represent is relatively straightforward at a coarse geographical scale, but can reflect a variety of processes at finer scale.

First, although some mortality has been observed in duck farms, HPAIV H5N1 infections are generally far less pathogenic in domestic waterfowl than they are in chickens (25). A large proportion of domestic ducks can become infected with HPAIV H5N1 without showing apparent clinical signs (26), and can spread the virus without being noticed. This translates into a broad-scale match between the distribution of domestic ducks and areas where HPAIV H5N1 persisted throughout Asia (27,28). However, the role of domestic ducks is more complex when considering the diversity of situations and mechanisms by which they may locally contribute to HPAIV H5N1 spread and persistence. In Thailand for example, where the geographical match between free-grazing duck density and HPAI H5N1 outbreaks is one of the strongest in all Asia, it is still unclear by which mechanisms free-grazing ducks can transmit the disease to other domestic poultry. Free-grazing ducks do not generally enter chicken farms and have a specific network of farming and trading. They are kept for limited periods as large flocks on post-harvest rice paddy fields and often transported by truck between fields. Another example is south Asia where the only region where HPAIV H5N1 has spread at a broad geographical scale corresponds to the area where domestic ducks are raised (27). However, within the main duck raising area in Bangladesh, Loth et al. (2010) in their finer-scale study did not find a statistical association between HPAI H5N1 risk and domestic duck density. A similar result was found in Indonesia: the majority of outbreaks have been reported in Java, which hosts the highest number of domestic ducks, but Loth et al. (2011) failed to identify a significant association between domestic duck density and HPAI H5N1 risk. Clearly, ducks play an important role in HPAIV H5N1 persistence to the extent that despite having been introduced to more than 60 countries, HPAIV H5N1 only persisted in those that have a high density of domestic ducks. But the extent by which they actively contribute to the transmission of the disease may vary considerably depending on the specific local conditions of farming and trading, which themselves vary considerably throughout Asia.

Second, anthropogenic variables were also frequently identified as important predictors of HPAI H5N1 risk. However, human population density is a proxy for a variety of possible mechanismss. The association of HPAI H5N1 risk with human population density could simply reflect a higher probability of detection in populated places. An outbreak taking place in a populated area, or near an important road, is much less likely to be detected than one located in remote areas. However, human population density was identified as a strong risk factor even in a country such as Thailand that applied extensive active detection surveys involving several hundred thousand surveyors searching door-to-door for evidence of HPAIV H5N1 infection even in small and remote villages, so it may reflect other mechanisms. Populated places also correspond to more intensive poultry trading and marketing activities that may support increased risk of transmission, either through the marketing of infected and apparently health poultry, or through contaminated fomites. This could be confirmed by social network studies that have recently been undertaken, and where some preliminary results suggest a statistical association between the connectivity of markets and HPAI H5N1 risk in China and Vietnam (29,30).

Third, although they were not always included in risk factor studies, variables indicative of the presence of water were repeatedly found to be associated with HPAI H5N1 risk. However, in multivariate studies, these variables were generally found to have lower statistical significance levels than domestic ducks and people. Water is an integral part of waterfowl habitat, and one may first consider that water-related variables are only a proxy allowing to spatially predict where domestic and wild waterfowl tend to concentrate. However, Thailand had extremely fine-scale data on their domestic duck population (administrative level 3, sub-districts with a median size of 16 km^2), and yet the presence of water (or a high cropping intensity which is only possible with a dense irrigation network) was found to be an important risk factor in different multivariate analyses. One can therefore hypothesise that water may have a direct causal link with HPAI H5N1 risk, for example by supporting transmission through contaminated water, where the virus can remain infective several days even at temperatures encountered in Southeast Asia (31). This would partly resolve some of the unknowns regarding the transmission between domestic ducks and other domestic poultry species, in particular chickens. These could, for example, become infected by drinking water from an irrigation canal which had been contaminated by upstream ducks shedding virus.

Several other factors were found to be associated with HPAI H5N1 risk, but the statistical significance and sign of the association was less constant across studies. The density of chickens, for example, is a variable that may cover a diversity of types of farming with extremely variable levels of bio-security, hygiene and disease prevention practices. Differences of the type of chickens (native vs. improved breeds), how they are raised (backyard vs. commercial), and how these differences were, or were not, accounted for in the cross-sectional studies likely explains the differences obtained across studies. If we consider China, for example, Martin et al. (2011) found a negative association between the presence of silent infection identified through active surveillance sampling and the density of chickens. This can be explained by the fact that intensively raised chicken farms located in the northern part of the country are subject to mass-vaccination that is more easily implemented under intensive farming conditions. Conversely, a positive association between chickens raised in farms and HPAI H5N1 risk was found by Loth et al. (2010) in Bangladesh, where semi-intensive farms still have relatively low levels of bio-security and means of disease prevention. Some case-control studies included in this review accounted for production systems and highlighted their respective effects. However, large-scale studies should be undertaken where poultry variables are broken down by production system categories that can account for the extremely diverse set of breeds and farming conditions encountered in Asia, and that reflect difference in terms of bio-security, hygiene, and investment in animal health.

Three types of factors have been poorly addressed in the studies reviewed here, especially if one considers their potential impact on disease transmission: i) socio-economic factors, ii) poultry trade factors, and iii) factors related to wild bird distribution. The common feature of all three factors is that there are technical difficulties in data collection. Socio-economic data (e.g. purchasing power per capita, land value, price indices) are often aggregated at a relatively coarse level, and can hence not be easily integrated into spatial modelling. Similarly, poultry trade variables are notoriously difficult to obtain. When available, these data ignore illegal trade, which is very significant in some countries, and that can be further exacerbated under HPAIV H5N1 epidemic conditions. Furthermore, trade patterns are extremely dynamic and can change according to production / demand discrepancies and price differences between geographic regions. A trade flow observed in a year between two regions could stop, or even reverse the following year as a result of changes in price differences between the regions. Some trade patterns, such as those driven by the demand of cities, are more predictable, but have yet rarely been accounted for. An example of predictable pattern is the Tet holidays, which can change temporarily the spatial pattern and intensity of trade flows (32).

Difficulty in obtaining pertinent spatial data is also one of the main reasons explaining why so few cross-sectional studies have formally integrated information on wild birds in HPAI H5N1 spatial modelling. In the wild avifauna, migratory water birds of the *Anatidae* family are those thought to have been implicated in long-distance transmission of HPAI H5N1. However, this family includes a large number of migratory species that have an inherently dynamic distribution. Data on their distribution in space and time are hence difficult to obtain at high resolution. Furthermore, although some sites are known to harbour large wintering populations, the precise locations where birds will actually stay may vary from year to year, depending on the specifics of the water level and food availability (33). One can then only predict areas where the birds are likely to be, rather than where they actually are (33). Massive efforts have been directed toward better characterisation of waterfowl migration patterns and habitat preference in the context of HPAI H5N1, and this has resulted in important advances in understanding their potential capacity to spread the virus over long distances (34). However, these data provide information on individuals that cannot easily be used to predict the distribution at the population level at a fine spatial scale.

Countries where HPAIV H5N1 has spread extensively have been covered by spatial modelling studies with a few noticeable exceptions. The most important one is Egypt, where the disease persists endemically and continues to cause human cases (35). Clearly, the Nile river delta where the disease is mostly concentrated in this country concentrates all three risk factors mentioned in this review based on studies carried out mainly in Asia: a very high density of domestic waterfowl, rural human population, and an abundance of water and irrigation networks. An analysis of the outbreaks would probably reveal similar associations, but could also highlight elements that are more specific to the Egyptian situation that may be helpful to help targeting disease prevention and control.

South Korea and Japan are two other countries where HPAI H5N1 occasionally re-emerges, with completely different conditions of poultry farming and trading involving intensive production and relatively high levels of bio-security and investment in animal health. In such a different context, spatial modelling of the disease’s spatio-temporal distribution may reveal complementary insight into the factors favouring the disease.

Future work could improve upon previous modelling findings in several ways. First, there has been much debate about the respective role of smallholders, semi-intensive and industrial farming in the HPAI H5N1 epidemics. The current body of studies that only rarely provides adequate differentiation of poultry data into different production system categories has not provided a robust evidence base to inform this debate. The same can be said about the respective role of wild birds and poultry trade in the spread of HPAI H5N1. We recognize the challenge of integrating these factors within the most commonly used modelling frameworks, and the challenge of obtaining pertinent data. However, with the emergence of the "One health" concept, that aims to more holistically integrate the key factors of the human and animal dimensions influencing emergence of infectious diseases, future work should aim at better integrating those overlooked factors into spatial models.

The integration of two other dimensions of ecological system within which HPAI H5N1 occurs should also be considered in future modelling efforts: time and evolution. With few exceptions, time has been ignored in previous studies and would deserve to be better accounted for in temporally explicit statistical modelling where both the dependent variable and the predictors are explicit in space and time. This could help quantifying the space-time association between the distribution of water, cropping or eco-climatic variables and HPAI H5N1 risk, and help developing hypotheses on the seasonality that was observed in HPAI H5N1 epidemic curves. Finally, all HPAI H5N1 cases have been considered molecularly and pathogenetically identical in the spatial modelling studies reviewed here, whilst the virus has evolved into a number of clades over time that could be linked to variations in pathogenicity and transmission (36). A better integration of phylogeographic and risk-factor type of studies, whilst methodologically challenging, would also provide much insight into the evolutionary conditions of emergence of this unprecedented panzootic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Xu X, Subbarao, Cox NJ, Guo Y. Genetic characterization of the pathogenic influenza A/Goose/Guangdong/1/96 (H5N1) virus: similarity of its hemagglutinin gene to those of H5N1 viruses from the 1997 outbreaks in Hong Kong. Virology. 1999 Aug.
2. Claas EC, Osterhaus AD, van Beek R, De Jong JC, Rimmelzwaan GF, Senne DA, et al. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. Lancet. 1998 Feb 14; 351(9101):472–477. [PubMed: 9482438]
3. FAO. [cited 2009 Jul 14] EMPRES-i Global disease information system [Internet]. 2009. Available from: http://empres-i.fao.org/empres-i/home
4. World Organization for Animal Health. World Animal Health Information Database (WAHID). 2011. Available on http://www.oie.int/wahis/public.php?page=home

5. Ostfeld RS, Glass GE, Keesing F. Spatial epidemiology: an emerging (or re-emerging) discipline. Trends Ecol. Evol. (Amst.). 2005 Jun; 20(6):328–336. [PubMed: 16701389]

6. Pfeiffer, DU.; Robinson, TP.; Stevenson, M.; Stevens, KB.; Rogers, DJ.; Clements, ACA. Spatial Analysis in Epidemiology. 1st ed.. OUP Oxford; 2008.

7. Gilbert M, Chaitaweesub P, Parakarnawongsa T, Premashthira S, Tiensin T, Kalpravidh W, et al. Free-grazing ducks and highly pathogenic avian influenza. Thailand. Emerg. Infect. Dis. 2006 Février;12(2):227–234.

8. Paul M, Tavornpanich S, Abrial D, Gasqui P, Charras-Garrido M, Thanapongtharm W, et al. Anthropogenic factors and the risk of highly pathogenic avian influenza H5N1: prospects from a spatial-based model. Vet. Res. 2010; 41(3):14. [PubMed: 19840537]

9. Tiensin T, Ahmed SSU, Rojanasthien S, Songserm T, Ratanakorn P, Chaichoun K, et al. Ecologic Risk Factor Investigation of Clusters of Avian Influenza A (H5N1) Virus Infection in Thailand. J. Infect. Dis. 2009 Jun 15; 199(12):1735–1743. [PubMed: 19416075]

10. Martin V, Pfeiffer DU, Zhou X, Xiao X, Prosser DJ, Guo F, et al. Spatial Distribution and Risk Factors of Highly Pathogenic Avian Influenza (HPAI) H5N1 in China. PLOS PATHOGENS. 2011 Mar.7(3)

11. Williams RAJ, Fasina FO, Peterson AT. Predictable ecology and geography of avian influenza (H5N1) transmission in Nigeria and West Africa. T. Roy. Soc. Top. Med. H. 2008 Mai;102(5): 471–479.

12. Williams RAJ, Xiao X-M, Peterson AT. Continent-wide association of H5N1 outbreaks in wild and domestic birds in Europe. GEOSPATIAL HEALTH. 2011 Mai;5(2):247–253. [PubMed: 21590675]

13. Williams RAJ, Peterson AT. Ecology and geography of avian influenza (HPAI H5N1) transmission in the Middle East and northeastern Africa. Int. J. Health. Geogr. 2009 Jul 20.8:47. [PubMed: 19619336]

14. Paul M, Wongnarkpet S, Gasqui P, Poolkhet C, Thongratsakul S, Ducrot C, et al. Risk factors for highly pathogenic avian influenza (HPAI) H5N1 infection in backyard chicken farms, Thailand. ACTA TROPICA. 2011 Juin;118(3):209–216. [PubMed: 21459074]

15. Henning J, Pfeiffer DU, Vu LT. Risk factors and characteristics of H5N1 Highly Pathogenic Avian Influenza (HPAI) post-vaccination outbreaks. Vet. Res. 2008; 40(3):15. [PubMed: 19081006]

16. Loth L, Gilbert M, Osmani MG, Kalam AM, Xiao X. Risk factors and clusters of Highly Pathogenic Avian Influenza H5N1 outbreaks in Bangladesh. Prev. Vet. Med. 2010 Aug l; 96(l–2): 104–113. [PubMed: 20554337]

17. Loth L, Gilbert M, Wu J, Czarnecki C, Hidayat M, Xiao X. Identifying risk factors of highly pathogenic avian influenza (H5N1 subtype) in Indonesia. Preventive Veterinary Medicine [Internet]. 2011 In Press, Corrected Proof. Available from: http://www.sciencedirect.com/science/article/pii/S016758771100208X.

18. Yupiana, Y.; de Vlas, SJ.; Adnan, NM.; Richardus, JH. [cited 2010 Jul 21] Risk factors of poultry outbreaks and human cases of H5N1 avian influenza virus infection in West Java Province, Indonesia. Int J Infect Dis [Internet]. 2010 Jul 14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20637674

19. Hogerwerf L, Wallace RG, Ottaviani D, Slingenbergh J, Prosser D, Bergmann L, et al. Persistence of highly pathogenic avian influenza H5N1 virus defined by agro-ecological niche. Ecohealth. 2010 Jun; 7(2):213–225. [PubMed: 20585972]

20. Biswas PK, Christensen JP, Ahmed SSU, Das A, Rahman MH, Barua H, et al. Risk for Infection with Highly Pathogenic Avian Influenza Virus (H5N1) in Backyard Chickens, Bangladesh. Emerg. Infect. Dis. 2009 Décembre;15(12):1931–1936. [PubMed: 19961672]

21. Ward MP, Maftei D, Apostu C, Suru A. Environmental and anthropogenic risk factors for highly pathogenic avian influenza subtype H5N1 outbreaks in Romania: 2005–2006. Vet. Res. Commun. 2008 Jun; 32(8):627–634. [PubMed: 18528778]

22. Cao C, Xu M, Chang C, Xue Y, Zhong S, Fang L, et al. Risk analysis for the highly pathogenic avian influenza in Mainland China using meta-modeling. Chin. Sci. Bull. 2010 Dec; 55(36):4168–4178.

23. Iglesias I, Jesus Munoz M, Martinez M, de la Torre A. Environmental Risk Factors Associated with H5N1 HPAI in Ramsar Wetlands of Europe. AVIAN DISEASES. 2010 Juin;54(2):814–820. [PubMed: 20608524]

24. Si Y, Wang T, Skidmore AK, de Boer WF, Li L, Prins HH. Environmental Factors Influencing the Spread of the Highly Pathogenic Avian Influenza H5N1 Virus in wild birds in Europe. Ecology and Society. 2010; 15(3):26.

25. Kwon H-I, Song M-S, Pascua PNQ, Baek YH, Lee JH, Hong S-P, et al. Genetic characterization and pathogenicity assessment of highly pathogenic H5N1 avian influenza viruses isolated from migratory wild birds in 2011, South Korea. Virus Res [Internet]. 2011 Jul 12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21782862.

26. Hulse-Post DJ, Sturm-Ramirez KM, Humberd J, Seiler P, Govorkova EA, Krauss S, et al. Role of domestic ducks in the propagation and biological evolution of highly pathogenic H5N1 influenza viruses in Asia. P. Natl. Acd. Sci. USA. 2005; 102(30):10682–10687.

27. Gilbert M, Newman SH, Takekawa JY, Loth L, Biradar C, Prosser DJ, et al. Flying Over an Infected Landscape: Distribution of Highly Pathogenic Avian Influenza H5N1 Risk in South Asia and Satellite Tracking of Wild Waterfowl. EcoHealth [Internet]. 2011 Jan. Available from: http://www.springerlink.com/content/emp41k2g37870611/.

28. Van Boeckel TP, Prosser D, Franceschini G, Biradar C, Wint W, Robinson T, et al. Modelling the distribution of domestic ducks in Monsoon Asia. Agric Ecosyst Environ. 2011 May l; 141(3–4): 373–380. [PubMed: 21822341]

29. Soares Magalhães RJ, Ortiz-Pelaez A, Thi KLL, Dinh QH, Otte J, Pfeiffer DU. Associations between attributes of live poultry trade and HPAI H5N1 outbreaks: a descriptive and network analysis study in northern Vietnam. BMC Vet. Res. 2010; 6:10. [PubMed: 20175881]

30. Martin V, Zhou X, Marshall E, Jia B, Fusheng G, Francodixon MA, et al. Risk-based surveillance for avian influenza control along poultry market chains in South China: The value of social network analysis. Preventive Veterinary Medicine [Internet]. 2011 Sep 16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21925753.

31. Nazir J, Haumacher R, Ike A, Stumpf P, Bohm R, Marschang RE. Long-term study on tenacity of avian influenza viruses in water (distilled water, normal saline, and surface water) at different temperatures. Avian Dis. 2010 Mar; 54(l Suppl):720–724. [PubMed: 20521721]

32. Pfeiffer DU, Minh PQ, Martin V, Epprecht M, Otte MJ. An analysis of the spatial and temporal patterns of highly pathogenic avian influenza occurrence in Vietnam using national surveillance data. Vet. J. 2007 Sep; 174(2):302–309. [PubMed: 17604193]

33. Cappelle J, Girard O, Fofana B, Gaidet N, Gilbert M. Ecological modeling of the spatial distribution of wild waterbirds to identify the main areas where avian influenza viruses are circulating in the Inner Niger Delta, Mali. Ecohealth. 2010 Sep; 7(3):283–293. [PubMed: 20865438]

34. Gaidet N, Cappelle J, Takekawa JY, Prosser DJ, Iverson SA, Douglas DC, et al. Potential spread of highly pathogenic avian influenza H5N1 by wildfowl: dispersal ranges and rates determined from large-scale satellite telemetry. Journal of Applied Ecology. 2010 Oct 1; 47(5):1147–1157.

35. Abdelwhab EM, Hafez HM. An overview of the epidemic of highly pathogenic H5N1 avian influenza virus in Egypt: epidemiology and control challenges. Epidemiol. Infect. 2011 May; 139(5):647–657. [PubMed: 21281550]

36. Pfeiffer DU, Otte MJ, Roland-Hoist D, Inui K, Tung N, Zilberman D. Implications of global and regional patterns of highly pathogenic avian influenza virus H5N1 clades for risk management. Veterinary Journal (London, England: 1997) [Internet]. 2011 Jan 31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21288747.

Table 1

Papers studying HPAI H5N1 spatial distribution grouped by geographical extent, and characterized by study area, type (CC: case-control; CS: cross-sectional; Desc: Descriptive; SP: Spatio-temporal pattern analysis), unit of analysis (Adm. L3: administrative level 3 boundaries or centroid), and analysis method (Log. Reg: logistic regression; Possion Reg. : Poisson regression; ENN: Ecological Niche Modelling; Space-time per.: Space-time permutation test)

Type	Study area	Unit of analysis	Method of analysis	Authors
Sub-national				
CC	Bangladesh	Farm	Log. Reg.	Biswas et al. (2009)
CC	Nigeria	Farm	Log. Reg.	Fasina et al. (2011)
CC	Indonesia	Market	Log. Reg.	Indriani et al. (2010)
CC	Thailand	Farm	Log. Reg.	Paul et al. (2011)
CS	Mekong Delta	Adm. L3	Log. Reg.	Henning et al. (2008)
CS	Indonesian Province	Adm. L3	Poisson Reg.	Yupiana et al. (2010)
National				
Desc.	Bangladesh	Cases	-	Ahmed et al. (2011)
Desc.	Nigeria	Cases	-	Cecchi et al. (2008)
Desc.	Indonesia	Cases (human)	-	Eyanoer et al. (2011)
Desc.	Thailand	Adm. L3	-	Tiensin et al. (2007)
SP	Bangladesh	Cases	K-function	Ahmed et al. (2010)
SP	Romania	Cases	Geostatistics	Farnsworth & Ward (2009)
SP	Vietnam	Adm. L3	K-function	Minh et al. (2009)
SP	China	Cases	Odens' direction	Oyana et al. (2006)
SP	Thailand	Adm. L3	Geostatistic test	Souris et al. (2010)
SP	Romania	Cases	Geostatistics	Ward et al. (2008)
SP	Southeast Asia & China	Cases (human)	Log. Reg	Kuo et al. (2009)
SP	China	Cases	Custom Model	Li et al. (2004)
CS	China	Cases	Log. Reg.	ChunXiang et al. (2010)
CS	China	Adm. L3	Log. Reg.	Fang et al. (2008)
CS	Thailand	Adm. L3	Log. Reg.	Gilbert et al. (2006)
CS	South Asia	Adm. L3	Log. Reg.	Gilbert et al. (2011)
CS	Bangladesh	Adm. L3	Log. Reg.	Loth et al. (2010)
CS	China	Adm. L3	Log. Reg., BRT	Martin et al. (2011)
CS	Thailand	Adm. L3	Log. Reg.	Paul et al. (2010)
CS	Vietnam	Adm. L3	Log. Reg.	Pfeiffer et al. (2007)
CS	Nigeria	Farm	Reg.	Rivas et al. (2010)
CS	Thailand	Adm. L3	Log. Reg.	Tiensin et al. (2009)
CS	Romania	Cases	Reg.	Ward et al. (2009)
CS	Romania	Cases	Log. Reg.	Ward et al. (2008b)
CS	Indonesia	Cases	Log. Reg.	Loth et al. (2011)

Type	**Study area**	**Unit of analysis**	**Method of analysis**	**Authors**
Regional / continental				
Desc.	Europe	Cases	-	Ottaviani et al. (2010)
Desc.	Eurasia	Cases	-	Gilbert et al. (2006)
Desc.	Asia	Country	-	Park et al. (2007)
Desc.	Eurasia & Africa	Cases	-	Sengupta et al. (2007)
SP	Eurasia & Africa	Cases (wild birds)	Space-time per.	Si et al. (2009)
SP	Eurasia & Africa	Cases	K-function	Liang et al. (2011)
SP / RF	Europe	Cases	ANOVA	Reperant et al. (2010)
CC	Europe	Wetland	Log. Reg.	Iglesias et al. (2010)
CS	SouthAsia	4 km	ENN	Adhikari et al. (2009)
CS	SouthAsia	Adm. L3	Log. Reg.	Gilbert et al. (2008)
CS	Europe	Cases (wild birds)	Log. Reg.	Si et al. (2010)
CS	NorthAfrica	Cases (8 km)	ENN	Williams & Peterson (2009)
CS	Nigeria	Cases (1 km)	ENN	Williams et al. (2008)
CS	Europe	Cases	ENN	Williams et al. (2011)
Global				
Desc.	-	Country	-	Kilpatrick et al. (2006)
CS	-	Country	Log. Reg.	Hogerwerf et al. (2010)

Table 2

Type of factors considered in case-control and cross-sectional studies on HPAI H5N1.

Papers	**Farming / biosecurity**	**Poultry / livestock**	**Anthropogenic**	**Socio-Economic**	**Wild birds**	**Rivers / lakes / wetlands**	**Ecoclimatic**	**Land-use / Cropping**	**Topographic**
Sub-national									
Biswas et al. (2009)	x	x	x		x	x			
Fasina et al. (2011)	x	x			x	x			
Henning et al. (2009)		x	x	x		x	x	x	
Indriani et al. (2010)	x	x	x						
Paul et al. (2011)	x	x	x	x		x		x	X
Yupiana et al. (2010)		x	x			x		x	
National									
ChunXiang et al. (2010)			x		x	x	x		
Fang et al. (2008)		x	x		x	x			
Gilbert et al. (2006)		x	x			x	x	x	X
Loth et al. (2010)		x	x					x	
Loth et al. (2011)		x	x			x		x	X
Martin et al. (2011)		x	x			x		x	X
Paul et al. (2010)		x	x			x		x	X
Pfeiffer et al. (2007)		x	x			x	x	x	X
Rivas et al. (2010)		x	x						
Tiensin et al. (2009)		x	x	x	x				
Ward et al. (2008b)			x			x		x	
Ward et al. (2009)					x				
Regional / continental									
Adhikari et al. (2009)			x				x		x
Gilbert et al. (2008)		x	x					x	x
Gilbert et al. (2011)		x	x					x	x
Iglesias et al. (2010)						x	x	x	
Reperant et al. (2010)					x		x		

Papers	Farming / biosecurity	Poultry / livestock	Anthropogenic	Socio-Economic	Wild birds	Rivers / lakes / wetlands	Ecoclimatic	Land-use / Cropping	Topographic
Si et al. (2010)		x	x			x	x		x
Williams & Peterson (2009)							x		x
Williams et al. (2008)							x		x
Williams et al. (2011)							x		
Global									
Hogerwerf et al. (2010)		x	x	x					
Total	4	19	21	4	7	14	11	13	11

Table 3

Sign and significance of the case-control and cross-sectional studies of HPAI H5N1, grouped by type of factors: +++, ++, and + refer to positive association with HPAI H5N1 presence significant at the p-level of < 0.001, < 0.01 and <0.05, respectively; conversely, minus sign are coded in the same way, but reflects negative association with HPAI H5N1 outcomes. Significance code and signs are presented in the same sequence as the corresponding references.

Risk Factors	**Significance / Sign**	**Country**	**Reference(s)**
Farming / Biosecurity			
Chicken and ducks in different shelters	− −	Bangladesh	Biswas et al. (2009)
Feeding with slaughter remnants of purchased chickens	+	Bangladesh	Biswas et al. (2009)
Bird slaughtering in live bird markets	+	Indonesia	Indriani et al. (2010)
Clear Zoning in LBM	−	Indonesia	Indriani et al. (2010)
Daily Solid Waste disposal	−	Indonesia	Indriani et al. (2010)
Slaughterhouses in Subdistrict	++	Thailand	Tiensin et al. (2009)
Purchase of live poultry from another farm	+++, ++	Thailand, Nigeria	Paul et al. (2011), Fasina et al. (2011)
Use of disinfectant to clean poultry area	−	Thailand	Paul et al. (2011)
Receive visitors on premises	++	Nigeria	Fasina et al. (2011)
Workers live outside premises	++	Nigeria	Fasina et al. (2011)
Time spent with the fighting cock	− −	Thailand	Paul et al. (2011)
Poultry / livestock			
Poultry flock density	++	Vietnam	Henning et al. (2009)
Poultry density	− − −	Indonesia	Yupiana et al. (2010)
Native chickens density	+++, − − −, +/−[1], +++	Thailand	Gilbert et al. (2006), Tiensin et al. (2009), Paul et al. (2010), Paul et al. (2011)
Chicken density	+, +/−, − − −, +++	Vietnam, World, China, South Asia	Pfeiffer et al. (2007), Hogerwerf et al. (2010), Martin et al. (2011), Gilbert et al. (2011)
Number of commercial chickens	++	Bangladesh	Loth et al. (2010)
Free-grazing duck density/ domestic duck density / domestic waterfowl density	+++,+,+++,+++,+,+++,++,+++	Thailand, Vietnam, World, China, South Asia	Gilbert et al. (2006), Pfeiffer et al. (2007), Gilbert et al. (2008), Tiensin et al. (2009), Paul et al. (2010), Hogerwerf et al. (2010), Martin et al. (2011), Gilbert et al. (2011)
Density of farm ducks	+	Thailand	Paul et al. (2010)
Duck by chicken density	+	Global	Hogerwerf et al. (2010)
Cock density	+++, ++, +/−	Thailand	Gilbert et al. (2006), Tiensin et al. (2009), Paul et al. (2010)
Quail flocks in subdistrict	+	Thailand	Tiensin et al. (2009)

Risk Factors	**Significance / Sign**	**Country**	**Reference(s)**
Buffalo density	− − −	Vietnam	Henning et al. (2009)
Anthropogenic			
Human population density	+++, ++, ++/− −, +, +++, +++, +++	Thailand, Vietnam, Bangladesh, China, South Asia, Indonesia	Gilbert et al. (2006), Gilbert et al. (2008), Tiensin et al. (2009), Loth et al. (2010), Yupiana et al. (2010), Martin et al. (2011)
Urban population density	++	Indonesia	Loth et al. (2011)
Rural population density	++	Indonesia	Loth et al. (2011)
Agricultural population density	+	Global	Hogerwerf et al. (2010)
Population density > 100 person / km2	N.A.	South Asia	Adhikari et al. (2009)
Distance to the nearest city	+/−, −, −, −	Thailand, Indonesia	Pfeiffer et al. (2007), Paul et al. (2010), Paul et al. (2011), Loth et al. (2011)
Min. distance to highway	− − −, +, − − −, − − −	China, Thailand, China, China	Fang et al. (2008), Paul et al. (2010), ChunXiang et al. (2010)
Roads density, presence of a road, road length	++, +, +, +++, +++	Bangladesh, Thailand, Romania, Indonesia	Ward et al. (2008b), Loth et al. (2010), Paul et al. (2010), Yupiana et al. (2010), Loth et al. (2011)
Socio-Economic			
% Housholds with electricity	− −	Vietnam	Henning et al. (2009)
Purchasing power per capita	−	Global	Hogerwerf et al. (2010)
Wild Birds			
Contact with resident birds	+	Bangladesh	Biswas et al. (2009)
Rivers / Lakes / Wetlands			
Access to water	+	Bangladesh	Biswas et al. (2009)
Min. distance to lake*Min distance to wetland	− − −	China	Fang et al. (2008)
Min. distance to reservoir / river / lake	−	China	ChunXiang et al. (2010)
Presence of a river stream, or flooded land area	++	Romania	Ward et al. (2008b)
Proportion of land occupied by water	−, +	Indonesia, China	Yupiana et al. (2010), Martin et al. (2011)
Presence of a pond or canal around farmhouse	+++	Thailand	Paul et al. (2011)
Mixosaline water (for wetlands only)	+++	Europe	Iglesias et al. (2010)
Eco-climatic			
Mean annual temperature range 21–26°C	N.A.[2]	SouthAsia	Adhikari et al. (2009)
January minimum temperatures (WB[3])	+++	Europe	Si et al. (2010)
Annual precipitation	− − −	China	Fang et al. (2008)

Risk Factors	**Significance / Sign**	**Country**	**Reference(s)**
January precipitations (WB)	− − −	Europe	Si et al. (2010)
May–Oct NDVI	−, ++	Vietnam	Pfeiffer et al. (2007), Henning et al. (2009)
March NDVI (WB)	+++/− − −	Europe	Si et al. (2010)
December NDVI (WB)	+++	Europe	Si et al. (2010)
High variation in NDVI	N.A., N.A.	SouthAsia, North Africa	Adhikari et al. (2009), Williams & Peterson (2009)
High NDVI	N.A.	North Africa	Williams & Peterson (2009)
Land use and cropping			
Cropping intensity	+++, +, +++	Thailand, Vietnam, Indonesia	Gilbert et al. (2008), Paul et al. (2010), Loth et al. (2011)
% land used for rice	+	Vietnam	Pfeiffer et al. (2007)
% area used for aquaculture	+	Vietnam	Pfeiffer et al. (2007)
Sweet potato yield	− − −	Vietnam	Henning et al. (2009)
Forestry (for wetlands)	+++	Europe	Iglesias et al. (2010)
Topography			
Elevation	− − −/+++, −/+, − − −, − −/++, −/+, − − −, − − −, − − −	Thailand, Vietnam, Europe, Indonesia	Gilbert et al. (2006), Pfeiffer et al. (2007), Gilbert et al. (2008), Tiensin et al. (2009), Paul et al. (2010), Si et al. (2010), Paul et al. (2011), Loth et al. (2011)
Low slope	N.A.	South Asia	Adhikari et al. (2009)

[1] the signs of −/+ refers to the signs of the single and quadratic term in linear models;

[2] N.A.: Not applicable because the method does not provide a significance *p*-value;

[3] WB: studies where only wild bird HPAI H5N1 data were analysed.