

1 **Spatiotemporal distribution of highly pathogenic avian influenza**
2 **subtype H5N8 in South Korea**

4 **Spatiotemporal analysis of HPAI H5N8**

5 Woo-Hyun Kim¹, Sun Hak Bae², Seongbeom Cho^{1*}

6 *¹College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National*
7 *University, Seoul, Republic of Korea,*

8 *²Department of Geography Education, Kangwon National University, Chuncheon, Republic of Korea*

11 * Correspondence

12 Seongbeom Cho, DVM, MPH, PhD

13 Professor

14 College of Veterinary Medicine

15 Seoul National University

16 1 Gwanak-ro, Gwanak-gu. Seoul 08826, KR

17 Tel: +82-2-880-1270

18 Fax: +82-2-880-1270

19 E-mail: chose@snu.ac.kr

Summary

In zoonotic disease, highly pathogenic avian influenza (HPAI) is a major threat to human and poultry health worldwide. In January 2014, HPAI virus subtype H5N8 first infected poultry farms in South Korea, and a total of 393 outbreaks were reported with enormous economic damage in the poultry industry. We analyzed the spatiotemporal distribution of HPAI H5N8 outbreaks in poultry farms using the global and local spatiotemporal interactions in the first outbreak wave from January 2014 to June 2015 and the second wave from September 2014 to June 2015. The space-time K-function analyses revealed significant interactions within three days and over 40 km in two study periods in global spatiotemporal interaction. The excess risk attributable value (D_0) was maintained despite the distance in the case of HPAI H5N8 in South Korea. Eleven spatiotemporal clusters were identified, and the results show the HPAI introduction from the southwestern region and the spread to the middle region in South Korea. Six clusters were distributed in 0.46-9.86 km space and 3-19 days in time, while five clusters were distributed in 19.74-72.59 km space and 27-36 days in time. This global and local spatiotemporal interaction indicates that the HPAI epidemic in South Korea was mostly characterized by short period transmission within a small area and dispersed by long-range jumps. This finding supports strict control strategies such as preemptive depopulation, the standstill, and poultry movement tracking. More studies are needed to understand HPAI disease transmission patterns of HPAI in South Korea.

Keyword: Avian influenza; Spatial Analysis; Spatiotemporal Analysis; H5N8 subtype

42 **Introduction**

43 Highly pathogenic avian influenza (HPAI) became a major zoonotic disease that threatens
44 public health (Alexander, 2007). The HPAI virus (HPAIV) is highly contagious to domestic
45 poultry and continuously occurs worldwide, causing enormous damage to the poultry
46 industry (Short et al., 2015). The HPAI subtype H5N8 infection in poultry farms was first
47 reported in January 2014 in South Korea (Lee, 2014). The results of a genetic epidemiologic
48 investigation showed that the transmission occurs through the migration pathway of wild
49 birds in winter season; indicating that the introduction of H5N8 HPAIV is associated with
50 wild waterbirds (Jeong et al., 2014). Migratory birds that stay in South Korea move through
51 the East Asia-Australia flyway, and the HPAI H5N8 virus has disseminated to other
52 continents, including Europe and United States, through the overlying flyways of migratory
53 birds (Verhagen, Herfst, & Fouchier, 2015).

54 While the wild migratory birds are the source of viral infection in domestic poultry farms
55 (Pandit, Bunn, Pande, & Aly, 2013), the HPAIV transmission and spread between farms
56 occurs mechanically through transport vehicles, people, feeds, clothes, shoes, and equipment
57 contaminated by dust, water, and feces of HPAIV-infected poultry (Dent, Kiss, Kao, &
58 Arnold, 2011). In a recent study, HPAIV airborne transmission can be possible between
59 poultry farms and may have played a role in spreading HPAI outbreaks in the United States
60 (Zhao et al., 2019). Considering these various HPAIV transmission pathways, it is important
61 to understanding how HPAI disease is transmitted through time and space to understand and
62 prevent the spread of disease.

63 The occurrence of space-time interactions between outbreak cases located close in time and
64 space varies and can be considered an infectious disease indicator (Diggle, Chetwynd,

Häggkvist, & Morris, 1995). Measuring and analyzing these indicators provide an understanding of the disease's underlying mechanisms, which enable the development of prevention strategies against disease spread (Baker, 2004). Space-time interaction analysis using the space-time K function has been used in the following animal disease studies: the foot-and-mouth disease in the United Kingdom (A Picado, Guitian, & Pfeiffer, 2007; Wilesmith, Stevenson, King, & Morris, 2003) and Tanzania (A. Picado et al., 2011), bovine tuberculosis in New Zealand (Porphyre, McKenzie, & Stevenson, 2007), Rift Valley fever in South Africa (Metras et al., 2012), and Africa swine fever in Russia Federation (Vergne, Gogin, & Pfeiffer, 2017). The spatiotemporal interaction of HPAI has been studied in France for the H5N8 subtype (Guinat et al., 2018) and in Vietnam for the H5N1 subtype (Loth, Pham, & Stevenson, 2019).

This study aimed to identify the time and space distribution of HPAI H5N8 outbreaks in South Korea from 2014 to 2016. The time-space interaction was analyzed using the space-time K function analysis and the scan statistics of HPAI transmission dynamics. It is believed that this systematic understanding of the spatiotemporal distribution will enable the evaluation of quarantine policies addressing the HPAI outbreaks, thereby providing scientific evidence for future policy development and suggesting the direction for further research.

Materials and Methods

Data collection and management

The epidemic data of HPAI subtype H5N8 were collected by the Animal and Plant Quarantine Agency (APQA) in Gimcheon, South Korea from January 15, 2014 to April 5, 2016 (Animal & plant Quarantine Agency, 2016). Following the identification of a bird with

clinical signs suspected of HPAI infection by the livestock owners, farm workers, and veterinarians, the case must be reported to the APQA according to the Act on Prevention of Contagious Animal Diseases (MAFRA, 2015) in passive surveillance. Veterinarians from governmental agencies visited the reported poultry farms to collect samples from the sick or dead birds, and then samples were tested to confirm possible HPAI infection. If the suspected farm was confirmed as HPAI-positive, it was deemed an infected premise (IP). Then infected poultry farms and neighboring farms located in a protective zone set to a radius of 3 km were depopulated. A depopulated farm found to be positive for HPAIV was referred to as a positive premise (PP) (Oh, 2018) in active surveillance.

In Korea, all the transporting vehicles related to the poultry industry for transporting either poultry, poultry products, medicines, feed, or feces must be registered with the Korea Animal Health Integrated System (KAHIS; <http://www.kahis.go.kr>). Based on these vehicles' geographical information, APQA conducted HPAI diagnostic test on the poultry farms visited by the vehicles entering HPAI-infected farms. This active epidemiological investigation of livestock-related vehicle movement makes it possible to detect additional HPAI-infected farms. In this study, all IPs and PPs found through this surveillance were considered as cases. All the geographical data of the poultry farms that were collected at the tong-ri administration, and village level, were projected to WGS84/UTM zone 52N (European Petroleum Survey Group; EPSG: 32652) and processed using QGIS (3.4) (QGIS Development Team, 2020). The dates of each case were based on the date of the first clinical signs observed.

Spatiotemporal analysis

HPAI subtype H5N8 outbreak from January 15, 2014 to April 5, 2016, was classified into four waves in Korea (Animal & plant Quarantine Agency, 2016). In this study, the first wave from January 15, 2014 to July 29, 2014, and the second wave that occurred from September 24, 2014 to June 10, 2015, were analyzed. The third (17 cases) and fourth waves (2 cases) of H5N8 were excluded due to the inadequate number of cases for the analysis.

Global and local spatiotemporal interaction analyses were conducted to describe the HPAI subtype H5N8's spatiotemporal characteristics between poultry farms in Korea. The global analysis used the space-time K function to calculate the spatiotemporal interactions of HPAI H5N8 outbreaks (Diggle et al., 1995). The space-time K function, $K(s,t)$, was defined as the number of expected cases (E) if cases are randomly- distributed within a distance s and a time t , then divided by the intensity λ , defined as the mean number of cases per unit of space and time (Equation 1).

$$K(s,t) = \lambda^{-1} E \quad (\text{Equation 1})$$

If cases occur independently in time and space without space-time interaction, $K(s,t)$ was the product of two K functions in space and time, similar to that shown in Equation 2.

$$K(s,t) = K(s) * K(t) \quad (\text{Equation 2})$$

We can define $D(s,t)$ as the difference between the observed and randomly expected space-time interactions (Equation 3);

$$D(s,t) = K(s,t) - K(s) * K(t). \quad (\text{Equation 3})$$

In this equation 3, $D(s,t) > 0$ means that space-time interactions are presented at a distance s and time t and with higher $D(s,t)$ values showing stronger evidence. D_0 was the value interpreted as the proportional increase, or excess risk attributable to the space-time

133 interaction to facilitate inference (Equation 4)

134
$$D_0(s,t) = D(s,t) / (K(s)*K(t)) \quad (\text{Equation 4})$$

135 $D_0(s,t) > 1$ indicated that the number of observed events was greater than twice the number of
136 expected events (Diggle et al., 1995; A Picado et al., 2007).

137 The null hypothesis of no space-time interaction in the observed cases was tested, the dates of
138 the cases were randomly permuted on a fixed set of the location of the cases, using Monte-
139 Carlo simulation, to generate a distribution of $D(s,t)$ to compare with the $D(s,t)$ of the
140 observed cases.

141 Suppose $D(s,t)$ value in the observed case exceeds 95% of values derived from the
142 simulation, in that case, we reject the null hypothesis because the probability of observed
143 space-time interaction occurring by chance is less than 5% probability. Therefore, it can be
144 concluded that there was a significant space-time interaction between the observed cases.

145 In this study, global spatiotemporal clustering of HPAI H5N8 outbreaks was investigated in
146 the first and second study periods using the space-time K function (Metras et al., 2012). The
147 space-time K function analysis was conducted using the maximum space-time window of 40
148 km and 40 days. Significant space-time clustering was simulated by generating 999 Monte-
149 Carlo random permutations. $D_0(s,t)$ value, the excess risk attributable to the space-time
150 interaction within a distance s and time t , was calculated and visualized in R software version
151 3.6 (R Core Team, 2020) using the ‘splancs’ package (Rowlingson & Diggle, 1993).

152 We used the space-time permutation model of the scan statistics to identify the local
153 spatiotemporal cluster of HPAI H5N8 outbreaks (Martin Kulldorff, 2007) by applying the
154 spatio-temporal windows shown in global spatiotemporal clustering. This approach was

based on creating a series of hypothetical spatiotemporal cylinder-centered coordinates of each case (M. Kulldorff, Heffernan, Hartman, Assuncao, & Mostashari, 2005). These cylinder bases and heights represent the space and time dimensions of each potential cluster, respectively. The approach to calculate cylinder is to iterate over a finite number and then gradually to increase the circle radius and height from zero to the maximum space and time value defined by the user. To test the null hypothesis, which assumed a no space-time interaction between cases, randomly distributed permutation of the spatial and temporal attributes of each case were performed using the Monte-Carlo simulation. Through this simulation, the expected disease occurrence is obtained when time and space are assumed to be independent of each other within a given space and time frame. If the observed actual cases are higher than the expected cases calculated through the above process, it can be inferred that the case in region within the cluster was more frequent in space and time than the rest of the geographic areas (M. Kulldorff et al., 2005; A. Picado et al., 2011; Porphyre et al., 2007).

The presence of local spatiotemporal clusters in HPAI H5N8 during the two study periods (first and second waves of the outbreaks) between the case poultry farms was investigated using the space-time permutation model of the scan statistic test, implemented using the SatScan (M. Kulldorff et al., 2005). Statistically significance reported at the level of 5% assessed by the 999 Monte-Carlo replications without overlapping. The maximum spatiotemporal window was set to 25% of the outbreak cases (first wave, 53 cases; second wave, 41 cases) and 25% of the study period (first wave, 49 days; second wave, 75 days).

Ethics Statement

178 The authors confirmed adherence to the ethical policies of the journal, as noted in the
179 journal's author guidelines. No ethical approval was required as this is an original article with
180 open-source data with Korea government.

181

182 **Results**

183 **Descriptive analysis**

184 In total, 393 HPAI subtype H5N8 outbreaks were reported in poultry farms from January 15,
185 2014 to April 5, 2016. Of these outbreaks, the first wave occurred from January 15, 2014 to
186 July 29, 2014 while the second wave was from September 24, 2014 to June 10, 2015. During
187 these two study periods, the majority of outbreaks were among the ducks (75.7%, 283/374),
188 followed by the chickens (20.9%, 78/374), and then others (3.5%, 13/374) such as quail or
189 ostriches. In the first (78.3%) and second waves (72.2%), the outbreaks mainly infected
190 ducks (Table 1).

191 HPAI H5N8 was distributed throughout, nationwide, but was mainly concentrated in the west
192 coastal and southern regions where the duck breeding density was high (Figure 1). The order
193 of the intensities of the distribution by province were Jeollanam-do (JN) (28.6%, 107/374),
194 Chungcheongbuk-do (CB) (24.9%, 93/374), and Jeollabuk-do (JB) (19.0%, 71/374). The
195 order of the case incidence rates was CB (27.4%), JB (22.2%), and JN (22.2%) in the first
196 H5N8 outbreak period; and JN (37.0%), CB (21.6%), and Gyeonggi-do (GG) (19.1%), in the
197 second outbreak period.

198 The temporal distributions of the first and second outbreaks of HPAI H5N8 in Korea are
199 shown in Figure 2. After the first case farm outbreak was reported on January 16, 2014, the

outbreaks increased continuously, peaked in February 2014, and only intermittently spread after March 20, 2014 (Figure 2A). The number of poultry farms infected during the exponential period was 178 (of 212 cases, 83.9%) in the first study period. In the second study period, the HPAIV was reintroduced to Korea on September 24, 2014, with a total of 61 farm outbreaks (37.6%, 61/162), which were infected exponentially for 34 days from January 28, 2015 to March 3, 2015 (Figure 2B).

Spatiotemporal analysis

Out of the 393 outbreaks of HPAI H5N8, a spatiotemporal analysis was performed on 212 and 162 farm outbreaks during the first and second study periods, respectively. The global spatiotemporal cluster of HPAI H5N8 in poultry farms was statistically significant ($p < 0.05$) for each study period (Figure 3). During the first study period (January 15, 2014 - July 29, 2014), the excess risk attributable to space-time interaction with $D_0 > 1$ was 40 km and three days; the time was closer to 0, and the D_0 value was higher (Figure 3A). The D_0 value was the highest (21.4) at the spatiotemporal parameters of 2 km and 0 days, and when the temporal parameter was set as 0 days, the D_0 value was maintained at 15, despite the increasing distance.

The excess risk attributable to the spatiotemporal interaction in the second study period (September 24, 2014- June 10, 2015) was 40 km and three days; the time was closer to 0, and the D_0 value was higher (Figure 3B). The excess risk attributable during the second period had a similar pattern to that of the first study period. The D_0 value was the highest (23.4) at 2 km and 0 days, and the value of 6 was maintained, despite the increasing distance.

We identified the 11 statistically significant spatiotemporal clusters from the result of the

space-time permutation scan statistic test. The geographical location of each cluster numbered according to the time of occurrence is indicated in Figure 4 and 5. The radius (km), temporal extension (days), number of outbreaks in the cluster, and the observed to the expected ratio of each cluster are shown in Table 2. The clusters were mainly formed around the west coastal area in South Korea. In the first study period, two clusters (Figure 4A) were formed in JN and JB, while three clusters were formed around the border areas of GG, CB, and CN (Figure 4B). The maximum spatial expansion of the clusters ranged from 2.21 km to 21.84 km, and the maximum time ranged from 3 to 30 days (Table 2). Since the cluster radius was the least at 2.21 km in cluster 3, but the number of farm outbreaks included in the cluster had the highest number of cases at 28. In the second study period, three clusters were found in JN and JB (Figure 5A), two clusters in the northern GG regions, and one cluster in the border areas of CB, CN, and GG (Figure 5B). The maximum space of the cluster was between 0.46 km and 72.59 km, while the duration was between 5 and 36 days (Table 2). All the clusters that showed statistically significant difference during the first study period overlapped with the epidemic exponential growth period (January 16 –March 20, 2014), while no statistically significant clusters were found that overlapped with the second exponential period (January 28 - March 3, 2015). Among HPAI poultry farms, during the study period, the proportion of farms in the cluster that were derived from the scan statistic test was 48.11% (102/212) in the first, and 51.23% (83/162) in the second.

Discussion

It is important to identify and analyze clustering to detect the area with a higher level of disease risk during outbreak investigations (Pfeiffer et al., 2008). There have been many

attempts to apply spatiotemporal modelling to zoonosis, which were estimating the space-time interaction between cases that are spatially and temporally proximate, make it possible to interpret the underlying transmission process (Ahmed, Ersbøll, Biswas, & Christensen, 2010; Guinat et al., 2018; A. Picado et al., 2011). Despite the importance of understanding the spatiotemporal disease dynamics, epidemiological research into HPAI epidemics in Korea was mainly focused on molecular investigations to track the origin of HPAIV strains and pathogens (Kwon et al., 2020; Si et al., 2016). It is important to analyze the global and local spatiotemporal interaction for the HPAI H5N8 outbreak to understand the disease transmission process for effective HPAI controls in poultry farms. This study investigated the spatiotemporal patterns of the first and second waves that occurred after the H5N8 HPAIV was introduced to Korea in January 2014. As far as we know, this is the first HPAI subtype H5N8 study in Korea that analyzed the global and local space-time interaction. This result will be a cornerstone in explaining the spatiotemporal factors related to HPAI H5N8 infection and transmission.

In space-time K function analysis, we identified space-time interactions over a distance of more than 40 km and under two days at the first study period (Figure 3 A). In addition, at 2 km and 0 days, the risk was highest and then decreased, maintaining a constant risk regardless of the increasing distance. This pattern of the space-time interaction was the same in the second study period, but the peak of the risk was highest at 0 days and 0 km, and the D_0 value decreased from 15 to 6 after two days (Figure 3 B). This results showed a different pattern from those of previous research (Guinat et al., 2018; Loth et al., 2019) that have analyzed the spatiotemporal analysis of other HPAs, and seems to be a characteristic of HPAI disease transmission in Korea. The results of the space-time K function analysis for HPAI in other countries showed significant spatiotemporal clustering less than 13 days and 8

km in France (Guinat et al., 2018), and less than 50 days and 60 km in Vietnam (Loth et al., 2019). Moreover, the excess risk reported in both studies showed a pyramidal shape in which the D_0 decreased as time and distance increased. Conversely, the excess risk was maintained even when the distance was increased in the spatiotemporal interaction in Korea (Figure 3). These results imply that the spread of HPAI disease in Korea occurs consistently regardless of the distance, especially within two days.

According to the results of our local spatiotemporal cluster analysis, HPAI from our two study periods tends to appear as the clusters in the western coastal area in Korea (Figure 4, 5). Five spatiotemporal clusters showed for 0.46-21.84 km and 5-28 days in JN and JB provinces (Figure 4B & 5B). Among them, the cluster 1 in each outbreak wave appeared in the early stage of outbreaks wave and the southwestern coastal area, major habitats of the wild migratory birds in the winter season. After introduction or re-introduction of HPAIV into Korea, six clusters of 2.21-72.59 km and 3-36 days were formed in the three provinces of GG, CB, and CN (Figure 4A, 5A). The assumption is that the HPAI introduced from the southwestern region has spread to the central area, considering the cluster formation time. These results of spatiotemporal clustering of HPAI H5N8 are consistent with the result of the origin and transmission H5N8 investigation by sequencing analysis, indicating that H5N8 virus entered to western coastal provinces and spread rapidly to other provinces with high densities of winter migratory birds and ducks holding (Hill et al., 2015). In light of these results, the HPAI intensive monitoring is necessary for these regions in winter seasons.

In our results, six clusters were distributed 0.46-9.86 km in space and 3-19 days in time, while five clusters were distributed 19.74-72.59 km in space and 27-36 days in time (Table 2). Furthermore, cluster 3 in the first study period and cluster 3 and 5 in the second study period were less than 3 km in size. It might be that this phenomenon appeared as the size of

clusters was suppressed by preemptive depopulation. On the contrary, 5 of the 11 clusters were covering the spatiotemporal extension from 27 to 36 days and from 19.74 to 72.59 km, which is larger than the period (10-25-days) and the distance (16.5 km-52.7 km) of the previous study on H5N8 spatiotemporal cluster study in France (Guinat et al., 2018). This shows that the regional spread of H5N8 in Korea was polarized between small and large spatiotemporal clusters. In other words, the HPAI virus disseminated in the extremely short distance and time, or rather spread over the long-distance and times.

Based on the results of the global and local spatiotemporal interaction, the following were assumed to have affected the spatial and temporal characteristics of the HPAI H5N8 in the poultry farms. First, we assumed that HPAI reporting and depopulation are carried out quickly in Korea, which leads to the prevention of adjacent disease spread (by the preemptive depopulation), from infected farms to the neighboring poultry farms. This can be inferred from the results showing that the time window of excess risk from the time-space interaction analysis was two days, which is shorter than the time reported in other studies (Guinat et al., 2018; Loth et al., 2019). In addition, the third cluster in the first period, the third and fifth clusters in the second period, had small spatial windows greater than 3 km. If the HPAI report from the poultry farms and the disease quarantine were delayed, HPAI would have had sufficient opportunity to propagate adjacent poultry holdings, which would have shown a similar spatiotemporal interaction of other studies (Guinat et al., 2018; Loth et al., 2019). According to APQA, when the suspected poultry with clinical signs is reported and confirmed positive, a 3 km radius depopulation is carried out around infected holdings, and this process, from report to depopulation, is conducted within a short period (Animal & plant Quarantine Agency, 2016). It can be inferred that the virus short-range contiguous transmission was blocked effectively by removing the host that could cause increase infection

spread.

Second, there is a high possibility that the cases that were due to the long-distance propagation of HPAI through vehicles were relatively due to oversampling, because of the suppression of the adjacent propagation of HPAI. The KAHIS was established in 2013 to integrate the management of animal disease and livestock quarantine information using information and communication technology (ICT) to prevent livestock disease outbreak (MAFRA, 2015). It is possible to collect information on registered vehicle movements related to the poultry industry, such as feces treatment, veterinarian visits, transporting of feed, medicine, poultry, and poultry products. It is mandatory to equip global positioning system (GPS) on registered vehicles under the Korean Act on the Prevention of Contagious Animal Diseases, and their movement information is periodically collected through KAHIS (Kim & Pak, 2019). This systemic tracking makes it possible to track the HPAI long-distance dissemination. If an HPAI case found through the long-distance propagation tracking using this mechanical relationship is included in the analysis, it is judged that a pattern of the D_0 value that is not affected by the distance in the spatiotemporal interaction can appear as shown in Figure 3. Therefore, this result of global spatiotemporal interaction is presumed to rapidly suppression of HPAI outbreaks through active surveillance.

Finally, the excess risk D_0 in the second study period was relatively reduced compared to the D_0 in the first study period (Figure 3). The factors that are estimated to have influenced the decrease in D_0 during the second study period are as follows. First, the livestock owners may be already aware of the HPAI introduction in poultry holdings during HPAI recurrence. Through this recognition, it can be assumed that alertness to HPAI has increased and faster disease reporting has been made. The effect of knowledge and awareness to HPAI reporting was reported from a study of HPAI during the 2006-2008 outbreaks in Nigeria (Ameji, Abdu,

Sa'idu, Kabir, & Assam, 2012). Second, the changed quarantine policy of the Korean government in the second period might be more effective in controlling the outbreak than in the first period. Due to continuous HPAI outbreaks in Korea, the Disease Outbreak Law and infectious disease standard operating procedure was revised in 2015 (MAFRA, 2015) and the systematic investigation of diseases was developed through the manual (Animal & plant Quarantine Agency, 2015). This change in HPAI biosecurity policy may have resulted in a reduction in excess risk attributable.

The finding of this study may have been affected by several limitations. First, there may have been cases where the presence of HPAI H5N8 was not reported if the sensitivity of the reports from the farms to the government were not optimal. In particular, in case of HPAI H5N8 in Korea, the infected ducks did not show clinical signs, which may have made the detection of H5N8 challenging (Kwon et al., 2020; Song et al., 2017). However, it is already mandatory to sample the poultry at the farm a day before transportation to other farms or slaughterhouses, to inspect them for HPAI using RT-PCR, since 2008 (MAFRA, 2015). Therefore, considering the massive HPAI inspection, the risk of unreported cases may be considered relatively low

Second, our analysis was performed on the assumption that the date when the clinical signs were first observed was the date HPAIV was first introduced into the poultry farm. This may have had effects on the study results because the incubation period of HPAI H5N8 may differ depending on the poultry species or the condition of the flocks. However, in our study periods, 75.7% of the cases included the ducks; therefore, it can be assumed that the latent period of H5N8 will be similar in most of the poultry farms. The interval from the date of the virus introduction to the flocks, to the date when the first clinical signs were observed is likely to be constant. Therefore, our assumption would not have a significant impact on the

temporal elements in our spatiotemporal analyses to the extent of results bias.

This study provides insights into the 2014-2016 Korea HPAI epidemic dynamics. This global and local spatiotemporal interaction indicates that the HPAI epidemic in Korea was mostly characterized by short period transmission within a small area and dispersed by long-range jumps. This disease transmission pattern is different from other HPAI spatio-temporal interaction studies. It is believed that these spatiotemporal analysis results are closely related to the rapid preemptive depopulation, standstill, and disease tracking policy, using GPS. This finding supports the need for strict control strategies such as the preemptive depopulation, the standstill of poultry transporting, and epidemiological movement tracking in Korea during the H5N8 disease period. Further research is needed to evaluate the optimal culling radius, the spread rate of disease between farms, and the disease transmission pathways by poultry-related vehicles, to help understand HPAI disease transmission patterns.

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Conflict of interest Statement

The authors have no conflicts of interest to declare.

Data availability

The data that support the findings of this study are available in 2014-2016 epidemiologic reports of highly pathogenic avian influenza at http://ebook.qia.go.kr/home/view.php?host=main&site=20161018_132952&listPageNow=0&list2PageNow=0&code=0&code2=0&

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482 **Table**

483 **Table 1.** Distribution of HPAI H5N8 outbreaks per species, type and period in Korea

Wave	Duck (%)	Chicken (%)	Others (%)	Total number of cases	Starts	End	Number of days
First	166 (78.3)	39 (18.4)	7 (3.3)	212	2014-01-15	2014-07-29	196
Second	117 (72.2)	39 (24.1)	6 (3.7)	162	2014-09-24	2015-06-10	260
Third	14 (82.4)	0 (0.0)	3 (17.6)	17	2015-09-14	2015-11-15	63
Fourth	2 (100.0)	0 (0.0)	0 (0.0)	2	2016-03-23	2016-04-05	14
Total	299 (76.1)	78 (19.8)	16 (4.1)	393			533

484 HPAI, highly pathogenic avian influenza

485

486 **Table 2.** Spatiotemporal cluster of Korea poultry farms during HPAI H5N8 outbreaks from 2014 to 2016

Wave	Cluster	Radius(km)	Start	End	Number of days	Number of outbreaks	Expected outbreak	Observe to expected ratio	<i>P</i> -value
First	1	9.86	2014-01-15	2014-01-24	10	20	2.3	8.8	0.001
	2	6.91	2014-02-01	2014-02-07	7	15	1.8	8.5	0.001
	3	2.21	2014-02-17	2014-02-19	3	28	4.1	6.8	0.001
	4	21.84	2014-03-10	2014-04-06	28	17	3.9	4.4	0.002
	5	19.74	2014-03-10	2014-04-08	30	11	2.2	5.1	0.030
Second	1	5.95	2014-09-24	2014-10-12	19	14	1.9	7.2	0.001
	2	72.59	2014-10-17	2014-11-19	34	11	2.3	4.8	0.025
	3	1.30	2014-12-22	2014-12-26	5	5	0.2	32.4	0.001
	4	19.76	2015-02-22	2015-03-20	27	36	10.2	3.5	0.001
	5	0.46	2015-03-26	2015-04-12	18	11	0.8	13.5	0.001
	6	30.74	2015-04-16	2015-05-21	36	6	0.4	16.2	0.001

487 HPAI, highly pathogenic avian influenza

Figure Legends

Figure 1. Location of Highly pathogenic avian influenza case farms in the first and second waves

Red round dot is the outbreaks in poultry farms at the first wave from January 14, 2014 to June 23, 2014. Green rectangle dot is the outbreaks in poultry farms at the second wave from September 23, 2014 to June 24, 2015.

Province abbreviations are as follows; CB: Chungbuk, CN: Chungnam, GB: Gyeongbuk, GG: Gyeonggi, GN: Gyeongnam, GW: Gangwon, JB: Jeonbuk, JN: Jeonnam.

Figure 2. Epidemic curve of HPAI H5N8 from 2014-2015

A. Epidemic curve of the first wave of HPAI H5N8 from January 2014 to August 2014 in South Korea.

B. Epidemic curve of the second wave of HPAI H5N8 from September 2014 to July 2015 in South Korea.

HPAI, highly pathogenic avian influenza

Figure 3 Excess risk attributable to the space-time interaction (D_0) as a function of space and time

A. Excess risk attributable to the space-time interaction of the first wave of HPAI H5N8 from January 14, 2014 to June 23, 2014.

B. Excess risk attributable to space-time interaction of the second wave of HPAI H5N8 from

509 September 23, 2014 to June 24, 2015.

510 The red-shaded area show the space-time interaction for which the observed number of cases
511 was higher than twice the expected number, which assumes no space-time interaction ($D_0 > 1$).

512 HPAI, highly pathogenic avian influenza

513

514 Figure 4. Spatiotemporal cluster of poultry farms during the first wave of HPAI H5N8
515 outbreaks in Korea

516 The left map shows whole area of South Korea

517 A) Spatiotemporal cluster of the first wave of HPAI H5N8 in the western middle region.

518 B) Spatiotemporal cluster of the first wave of HPAI H5N8 in the southwestern region

519 Province abbreviations are as follows; CB: Chungbuk, CN: Chungnam, GB: Gyeongbuk,

520 GG: Gyeonggi, GN: Gyeongnam, GW: Gangwon, JB: Jeonbuk, JN: Jeonnam.

521 HPAI, highly pathogenic avian influenza

522

523 Figure 5. Spatiotemporal cluster of poultry farms during the second wave of HPAI H5N8
524 outbreaks in Korea

525 The left map shows whole area of South Korea

526 A) Spatiotemporal cluster of the second wave of HPAI H5N8 in the western middle region.

527 B) Spatiotemporal cluster of the second wave of HPAI H5N8 in the southwestern region

528 Province abbreviations are as follows; CB: Chungbuk, CN: Chungnam, GB: Gyeongbuk,

529 GG: Gyeonggi, GN: Gyeongnam, GW: Gangwon, JB: Jeonbuk, JN: Jeonnam.

530 HPAI, highly pathogenic avian influenza

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