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Author(s): P. Mulatti, U. Kitron, A. Mannelli, N. Ferrè and S. Marangon

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## Research Note—

## Spatial Analysis of the 1999–2000 Highly Pathogenic Avian Influenza (H7N1) Epidemic in Northern Italy

P. Mulatti,<sup>A</sup> U. Kitron,<sup>B</sup> A. Mannelli,<sup>C</sup> N. Ferrè,<sup>A</sup> and S. Marangon<sup>A</sup>

<sup>A</sup>Centro Regionale per l'Epidemiologia Veterinaria, Istituto Zooprofilattico Sperimentale delle Venezie, Viale dell'Università 10, 35020 Legnaro (Pd), Italy

<sup>B</sup>Department of Pathobiology, 2001 South Lincoln Avenue, Urbana, IL, 61801

<sup>C</sup>Dipartimento di Produzioni Animali, Epidemiologia ed Ecologia, Via Leonardo da Vinci 44, 10095 Grugliasco (To), Italy

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**SUMMARY.** The effect of proximity on infected premises was evaluated during the highly pathogenic avian influenza (HPAI) epidemic that struck northern Italy in 1999–2000 by quantifying the spatial and temporal clustering of cases. The epidemic was caused by an H7N1 subtype of type A influenza virus that originated from a low-pathogenic AI virus that spread among poultry farms in northeastern Italy in 1999 and eventually became virulent by mutation. More than 90% of 413 infected premises were located in Lombardy and Veneto regions; of 382 outbreaks, 60% occurred in the Lombardy region and 40% in the Veneto region. Global and local spatial statistics were used to estimate the location and degree of clustering of cases with respect to the population at risk. Outbreaks were spatially clustered primarily in Lombardy, with a large cluster in Brescia province and another in Mantua province, on the border of Veneto. Time series analysis was used to assess the temporal clustering of outbreaks. Temporal aggregation increased during the first 5 wk and decreased thereafter (probably as a result of eradication measures enforced in the Veneto region). Spatio-temporal clustering was assessed considering the Temporal Risk Window (TRW), the time period during which premises remain infectious and infection can spread to neighboring premises. The clustering pattern was similar to the one detected when considering spatial clustering (i.e., the larger clusters were identified in the Brescia and Mantua provinces of Lombardy). These results highlight the role of proximity in the spread of AI virus and, when considering the TRW, indicate the possible direction of virus spread.

**RESUMEN.** *Nota de Investigación*—Análisis espacial de la epidemia de influenza aviar de alta patogenicidad durante los años 1999 y 2000 en el norte de Italia.

Mediante la cuantificación del agrupamiento espacial y temporal de los casos, se evaluó el efecto de la proximidad de granjas infectadas durante la epidemia de influenza aviar de alta patogenicidad que afectó el norte de Italia durante los años 1999 y 2000. La epidemia fue causada por un subtipo H7N1 del virus de influenza aviar tipo A originado de virus de influenza aviar de baja patogenicidad que se diseminó en las granjas del noreste de Italia en el año 1999 y que eventualmente mutó a la forma virulenta. Más del 90% de las 413 granjas infectadas estaban localizadas en las regiones de Lombardia y Veneto; de un total de 382 brotes, el 60% ocurrieron en la región de Lombardia y el 40% en la región de Veneto. Se utilizó estadística local espacial con la finalidad de estimar la localización y el grado de agrupamiento de los casos con respecto a la población a riesgo. Los brotes se agruparon principalmente en Lombardia, con la presencia de un grupo grande en la provincia de Brescia y otro en la provincia de Mantua en la frontera con Veneto. Se utilizaron análisis de series de tiempo para evaluar el agrupamiento temporal de los brotes. La agregación temporal se incrementó durante las primeras cinco semanas y disminuyó a partir de allí (probablemente a consecuencia de las medidas de erradicación impuestas en la región de Veneto). El agrupamiento espacio-temporal se evaluó considerando la ventana de riesgo temporal, que es el periodo durante el cual las granjas permanecen positivas y la infección puede diseminarse a granjas vecinas. El patrón de agrupamiento fue similar al detectado cuando se evaluó el agrupamiento espacial (por ejemplo, los agrupamientos más grandes fueron identificados en las provincias de Brescia y Mantua en Lombardia). Estos resultados resaltan el papel de la proximidad entre las granjas en la diseminación del virus de influenza aviar e indican la posible dirección de la diseminación del virus cuando se considera la ventana de riesgo temporal.

**Key words:** avian influenza, spatial analysis, space–time analysis, hot spots

**Abbreviations:** AI = avian influenza; CSR = complete spatial randomness; HPAI = high pathogenicity avian influenza; IP = infected premises; IR = incidence rate; LPAI = low-pathogenicity avian influenza; TRW = temporal risk window

Spatial and temporal analyses of epidemiologic data provide clues in the understanding of the dynamics of disease spread in the population. The simplest theoretical model for a spatial analysis is that of complete spatial randomness (CSR), in which every location in the study region is a likely candidate for an event (such as an outbreak) to occur; in other words, the events are distributed independently according to a uniform probability distribution (usually a Poisson distribution) over the region of study (4). Space analysis allows us to detect the divergence from the CSR. In particular, global spatial analysis permits us to identify the clustering of the population of events as a whole, allowing us to hypothesize regarding the presence

of factors that determine aggregation of events in the whole area, such as environmental factors. However, global spatial analysis is not able to detect small clusters distributed randomly (i.e., in according to the CSR distribution). On the other hand, local spatial analysis studies the clustering of events with respect to other events, giving an idea of aggregation on a local level. This approach allows the identification of small clusters that are not affected by the interaction of events at a regional level.

With respect to the study of the epidemiology of a given infectious disease, clustering of infected premises (IP) during an epidemic can be the result of a nonrandom distribution of an at-risk population,

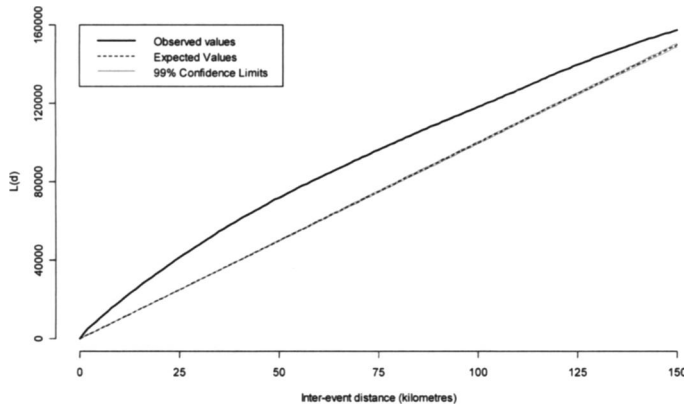


Fig. 1. Global spatial clustering of the flocks at risk evaluated through a linearized K function  $[L(d)]$ . The interevent distance at which the clustering is maximized is reported on the abscissa axis.

the result of certain risk factors, or the result of the particular effectiveness of some IP in virus transmission (superspreaders). Detection of spatial and space–time clusters is useful in generating hypotheses regarding risk factors and in identifying areas in which viral transmission is greater (hot spots) and, as a consequence, in which disease surveillance and control should be targeted.

The effect of proximity on IP was evaluated for the highly pathogenic avian influenza (HPAI) epidemic that struck northern Italy in 1999–2000. Measures of spatial, temporal, and space–time clustering of cases were calculated.

The epidemic was caused by an H7N1 subtype virus that originated in December 1999, through mutation, from a low-pathogenicity AI (LPAI) virus had been circulating among poultry farms since the spring of 1999 (2). From December 5, 1999, to April 5, 2000, 413 HPAI-affected poultry farms were detected. Most (382; 92.5%) of the HPAI outbreaks were concentrated in Lombardy and Veneto (5). The control measures provided for in the European legislation (92/40/EC) were enforced to eradicate the infection (3). In Veneto, where flock density was the highest, disease control was also accomplished through a ban on restocking and depopulation of susceptible flocks through preemptive slaughter of flocks that were in the vicinity or that had dangerous contacts with IP. In Lombardy, such control measures were applied to a lesser extent. The disease incidence rate (IR) was 2.6 and 1.1 cases per 1000 flocks per day in

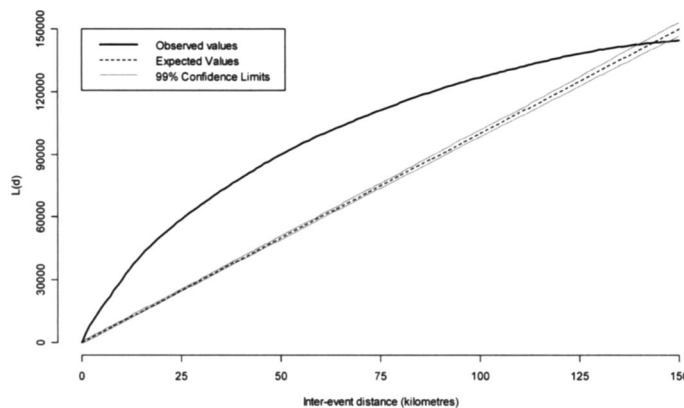


Fig. 2. Global spatial clustering of the IP evaluated through a linearized K function  $[L(d)]$ . The interevent distance at which the clustering is maximized is reported on the abscissa axis.

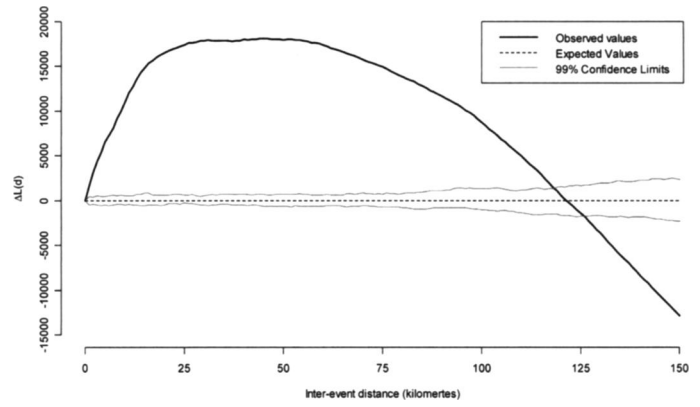


Fig. 3. Evaluation of the clustering of IP with respect to the distribution of the flocks, calculated through the difference between the  $L(d)$  of IP and the  $L(d)$  of flocks  $[\Delta L(d)]$ . The interevent distance at which the clustering is maximized is reported on the abscissa axis.

Lombardy and Veneto, respectively. The objectives of the study were to detect clusters and to identify those IP from which infection was most likely transmitted to neighboring flocks.

### MATERIALS AND METHODS

Spatial analyses were based on the precise location of poultry premises in Veneto and Lombardy regions, expressed in coordinates in the National Projection System (ED50, Gauss Boaga).

Global spatial analyses were carried out through the  $K$  function  $[K(d)]$ , which is used to analyze the distribution of both farms and outbreaks in Lombardy and Veneto regions.  $K$  function compares the distribution of farms and outbreaks (both considered “events”) to the one expected, as calculated by a CSR distribution. The  $K(d)$  can be estimated by the following formula:

$$K(d) = \frac{A}{n^2} \sum_{i=1}^n \sum_{j=1, j \neq i}^n I_d(h_{i,j})$$

where  $A$  is the area of the area of study;  $n$  is the number of cases in area  $A$ ;  $i$  and  $j$  are events of interest;  $h_{i,j}$  is the distance between  $i$  and  $j$ ;  $I_d(h_{i,j})$  is an indicator function that is equal to 1 if  $h_{i,j} \leq d$  and 0 otherwise.  $K(d)$  sums all the events that are within a distance  $d$  from each event (1). Clustering is graphically evaluated by comparing the estimated and the expected distributions of  $K(d)$ , previously linearized to  $L(d)$ . The linearization of  $K(d)$  distribution

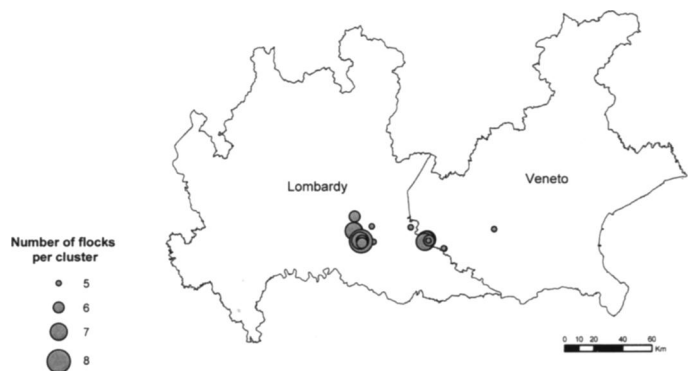


Fig. 4. Local spatial analysis—Significant local clustering of infected premises during the HPAI epidemic in Italy, 1999–2000.

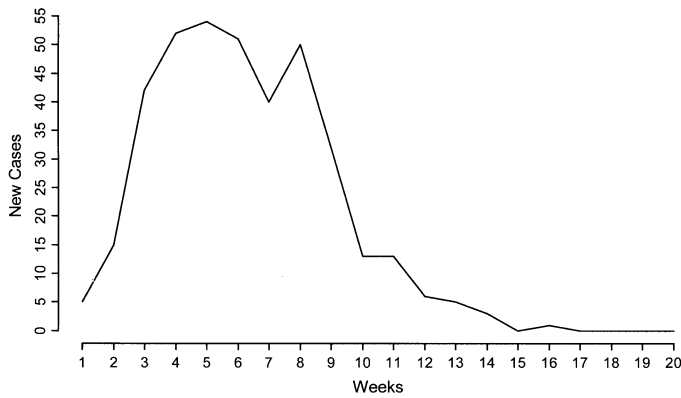


Fig. 5. Weekly incidence of the highly pathogenic avian influenza in Italy, 1999–2000 (number of new cases per week).



Fig. 6. Local space–time analysis—Location of the IP that generated space–time clusters during their TRW.

produces a  $L(d)$  that under the null hypothesis is  $L(d) = d(7)$ . If the observed  $L(d)$  exceeds the expectation at some scale, the pattern shows clustering, whereas if the expected exceeds the observation, the pattern observed follows a regular distribution, or, if it's equal to or between the confidence limits of the expected, it follows a CSR distribution. In order to take into account the effect of farm distribution in the two regions, the clustering was evaluated by plotting  $\Delta L(d)$ , that is, the difference between the distribution estimated for the IP and the one for the farms, obtaining a measure of clustering of IP with respect to the distribution of flocks (4).

As a measure of local spatial clustering, the number of IP that occurred within a radius of 1500 m from another IP was calculated. The cut-off of 1500 m was taken from the literature (5,8).

Statistical significance was tested using a Monte Carlo simulation with 99 permutations, rearranging the health status (i.e., if the flock was infected or not) among the whole population of flocks at risk and recalculating the statistic for each permutation. The null hypothesis was that the observed spatial pattern of IP could be explained by chance alone.

Temporal aggregation of cases was determined based on the number of new IP per week. Space–time clustering was tested by calculating the number of flocks located within a 1500-m radius from an IP that became new cases during the temporal risk window (TRW) of that IP. A TRW is defined as the time period during which it is possible to identify symptoms in a flock that was infected by transmission from an IP that is considered a neighbor (8). TRWs were calculated on the basis of the introduction of the virus in the IP (which was considered to occur 1 day before the first symptom of AI appeared on the premises) and the day in which the animals in the IP were slaughtered (duration of the TRW: minimum = 5 days; maximum = 52 days; median = 11 days).

The index of the number of new cases that were verified within a radius of 1500 m from an IP with an open TRW was calculated by the statistic  $Gr_i$ . The equation used was

$$Gr_i = \sum_{t=0}^T \sum_{j=1; j \neq i}^N r_{i,t} s_{j,t} d_{i,j}$$

where  $N$  is the number of flocks in the area at risk studied;  $t = 0$  is the first day of the epidemic, considered to be the day in which the first outbreak occurred;  $T$  is the last day of the epidemic, considered to be the same as the end of the last TRW period;  $r_{i,t}$  is equal to 1 if the IP  $i$  is in TRW at day  $t$  and 0 otherwise;  $s_{j,t}$  is equal to 1 if the flock  $j$  becomes an IP (i.e., shows its first symptoms) at day  $t$  and 0 otherwise; and  $d_{i,j}$  is equal to 1 if the flock  $j$  is within a 1500-m radius of the IP  $i$  and 0 otherwise. The analyses were carried out using the R software (version 2.2.0) and the R-packages *splan*, *spatstat*, and *spdep* (6).

## RESULTS

Global spatial analysis showed that both flocks and IP were clustered with respect to the area of study, with maximized clusterings at 56 km and 52 km, respectively (Figs. 1, 2). IP were more clustered than the population of poultry premises, with clustering maximized around 46 km (Fig. 3).

A total of 77 spatial clusters yielded a statistically significant result through the Monte Carlo simulations (number of flocks per cluster: minimum = 2; maximum = 8; median = 4). The clusters with more than four IP (Fig. 4) were mainly located in the Lombardy region, in particular in the Brescia and Mantua provinces.

Temporally, aggregation increased during the first 5 wk of the epidemic, followed by a decrease and a second peak around the eighth week; after that the number of new cases per week started to decrease until the 17th week and remained low from this point to the end of the epidemic (Fig. 5).

A total of 90 space–time clusters were detected (flock per cluster, in addition to the IP with an open TRW: minimum = 1; maximum = 4; median = 1). In contrast to spatial aggregation, the number of flocks per cluster was intended to represent the number of flocks that became infected within a radius of 1500 m from an IP with an open TRW, which was considered to be the cluster generator. The pattern of the largest space–time clusters (Fig. 6) showed a clear similarity to the one detected when considering spatial clustering alone, with a greater aggregation in the Lombardy region (more precisely, in the Brescia and Mantua provinces) on the border with Veneto.

## DISCUSSION

Global spatial analyses performed on both flocks and IP (Figs. 1, 2) resulted in a maximized clustering level at around 50 km. Since the clustering pattern appeared quite similar, factors such as the presence of mountains in the northern part of the regions should have forced the farms to be located in a fraction of the whole area of the regions. The IP appeared to be more clustered than the flocks (Fig. 3), but the maximized clustering (46 km) is around a distance that could hardly be considered to be within the proximity. On a regional level, then, proximity did not seem to have great importance, unlike other factors, such as environmental factors (for the distribution of the population) or the different types of contacts between IP.

Since global spatial analysis did not detect the presence of small clusters, local analyses were performed. Local cluster and space–time

analyses, considering a radius of 1500 m, allowed us to identify the most likely hot spots (i.e., zones in which the spread of the disease between farms most likely occurred). In particular, considering the TRW as a temporal dimension, it is possible to hypothesize that the virus spread from the space–time cluster generator IP to the other flocks that are in that cluster. Indeed, it is important to recall that the TRW is the period during which it is possible to identify symptoms in a flock that was infected by transmission from an IP that is considered a neighbor.

The time series analysis showed a first decrease after the fifth week of epidemic, which can be identified as the consequence of the ban on restocking and the depopulation policy adopted in Veneto, whereas the second peak coincided with the spread of disease in the Lombardy region. These results, together with the detection of the largest space–time clusters in Lombardy, provided information on the effectiveness of the sanitary measures adopted in the Veneto region compared with those adopted in Lombardy.

In conclusion, combining spatial, temporal, and space–time analyses to identify hot spots for viral transmission is a promising approach for surveillance, prevention, and control of possible future outbreaks and epidemics.

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