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**Evaluation of the risk of neighbourhood infection of H7N1 Highly Pathogenic
Avian Influenza in Italy using *Q* statistic**

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Abstract

Exposure to the risk of neighbourhood infection was estimated for the H7N1 Highly Pathogenic Avian Influenza (HPAI) epidemic that affected Northern Italy between 1999 and 2000. The two most affected regions (Lombardy and Veneto) were analyzed and the epidemic was divided into three phases. Q statistics were used to evaluate exposure to the risk of neighbourhood infection using two measures. First, a local Q statistic (Q_{ikt}) assessed daily exposure for each farm as a function of the number of neighbouring infected farms that were in their infectious period, weighted by the distance between farms. This allowed us to identify the daily time course of risk for each farm and, at any given time, local groups of farms defined by high risk. Second, for each farm a summary statistic of exposure risk within each phase (Q_i^{ph}) was obtained by summing Q_{ikt} over the duration of each phase. This allowed identification of farms defined by persistent, high exposure risk within each phase of the epidemic. Statistical significance was evaluated using conditional Monte Carlo simulation, and significant values of Q_i^{ph} were mapped to assess the variation of the risk of neighbourhood infection through the phases. Q_{ikt} was larger for farms in Lombardy and the reduction of exposed farms was more marked for Veneto. Although the highest value of Q_i^{ph} was observed in Veneto, in each phase most of the significant values were in Lombardy. In the last phase of the epidemic, a large reduction in the number of farms significantly exposed to the risk of neighbourhood infection was observed in the Veneto region, along with generally low values of Q_i^{ph} . This may be explained by differences in control measures in the two regions, including pre-emptive slaughtering of farms considered at high risk of infection. The Q statistic allowed us to quantify geographic, time-dynamic variations in exposure to

neighbourhood infection, and to generate hypotheses on the efficacy of control measures.

Keywords: spatial analysis, exposure, Temporal Risk Window, Avian Influenza

1. Introduction

A severe Highly Pathogenic Avian Influenza (HPAI) epidemic occurred in Italy from December 1999 to April 2000. A total of 413 HPAI infected farms were detected in less than 5 months, of which 392 (95%) were located in the northern regions of Lombardy (234/392, 59.7%) and Veneto (158/392, 40.3%) (Figure 1). The HPAI eradication measures provided for in The European Community Council Directive 92/40/EEC were promptly enforced, including pre-emptive slaughter of all poultry on infected farms (IFs) and restrictions of movement of live poultry, vehicles and staff (CEC, 1992). Pre-emptive slaughter of poultry farms was implemented in Veneto starting on 20 January 2000, involving a total of 68 farms (1,678,566 birds slaughtered). In Lombardy, pre-emptive slaughter was implemented three weeks later, starting on 10 February 2000, and only in 10 farms (354,234 birds slaughtered) (Figure 2). Criteria for pre-emptive slaughter were: location of farms within a radius of 1 km from an IF; dangerous contacts with an IF (e.g. introduction of animals or sharing of vehicles); and ownership of a farm by the same owner of another farm already found to be infected.

Proximity among farms is commonly used as a risk factor in epidemiological analysis and in the control of epidemic diseases of livestock, especially in the absence of accurate information on infectious contacts among farms (Elbers *et al*, 1999;

Crauwels *et al*, 2003). Moreover, the identification of clusters of transmission among neighbouring farms can provide useful information in disease prevention and control. The analysis of risk factors showed that proximity (<1500 m) to IFs in their infectious period strongly increased the risk of HPAI infection for poultry farms in Italy (Mannelli *et al*, 2006). Subsequently, Mulatti *et al* (2007) studied spatial and space-time clustering of HPAI by estimating the count of new IFs occurring within 1500 m of IFs that were in their infectious period. The greatest clustering levels were identified in the Lombardy region, in the area bordering Veneto. Potential transmission of infection among new IFs belonging to a cluster was, however, not taken into account.

In general, the analysis of clustering for highly contagious diseases, such as HPAI, is complicated by non-independence of cases. In this study, Q statistic (Jacquez *et al*, 2005, Jacquez and Meliker, 2009) was used since it relaxes the abovementioned assumptions. Here, the non-independence of IFs is not critical since IFs were considered as potential sources of infection for susceptible farms. The objectives were to (1) identify spatial and temporal variations of exposure to infectious IFs in order to quantify the risk of infection for susceptible farms, and (2) generate hypotheses regarding the efficacy of control measures, including depopulation of IFs and pre-emptive slaughter of poultry on at-risk farms.

2. Materials and Methods

2.1 Data sources

We analyzed a database containing information about the commercial poultry farms of the Veneto and Lombardy regions, North-eastern Italy (Figure 1). A total of 3,257 commercial poultry farms were included in the study. Due to the absence of reliable

information, backyard flocks were not considered in the population at risk, nor were the 10 involved backyard farms included in the analyses of the 392 outbreaks that occurred in Lombardy and Veneto. These infected backyard flocks had little or no contact with other farms, so their role in the disease spread was likely to be limited (Capua *et al*, 2003).

In accordance with the EU legislation in force at that time, a farm was considered an IF if the infection was confirmed by isolation of the AI virus or, later in the epidemic, if post-mortem lesions consistent with HPAI infection were observed. Suspected cases were notified by farmers to official veterinary services. Moreover, flocks that were considered at risk of infection based on the proximity (<1 km) to, or dangerous contacts with IFs, were inspected and laboratory analysis was carried out according to EU standards (CEC, 1992)

The hypothesized infectious period of each IF was modelled as a *Temporal Risk Window* (TRW). The TRW can be defined as the time period during which clinical signs could be identified in any other farm infected by transmission from the IF (Taylor *et al*, 2004). The TRW was calculated for each IF as following (Mannelli *et al*, 2006):

- *Start of TRW= Onset date – latent infectious period + minimum incubation period;*
- *End of TRW= Culling date + maximum incubation period;*

resulting in a distribution of TRWs with a minimum= 5 days; maximum= 52 days; and median=11 days. The latent infectious was considered as equal to 1 day, whereas the minimum and maximum incubation period were set as equal to 2 and 6 days respectively. A farm was considered exposed to the risk of being infected (thus manifesting HPAI symptoms) if at least one of the nearest neighbouring IF had an open TRW.

Geographical location, dates of restocking and slaughter for all the farms, and dates of detection of IFs were considered in the study. The study period (123 days) corresponded to the length of the epidemic, 5 December, 1999 to 5 April, 2000.

2.2 Q statistic

The Q -statistic was first used to describe and explain spatial and space-time clustering of chronic diseases in human medicine (Jacquez et al, 2005). The statistic relied on the concept of residential history of patients, i.e. the variation in time of the location of each patient, of nearest neighbours and of the exposure to potential risk factors.

The Q statistic was modified to suit the analysis of farm-based infection processes by taking temporal variation in the proximity between infectious IFs into account. A local Q statistic was then defined as:

$$Q_{ikt} = \sum_{j=1; j \neq i}^{N-1} \eta_{ijkt} c_{jt} w_{ij} ; \quad (1)$$

where $\eta_{i,j,k,t}$ is equal to 1 if the j th farm was one of the k -nearest neighbours of farm i at time t , and 0 otherwise; c_{jt} is equal to 1 when j is an IF in its TRW at time t , and 0 otherwise; w_{ij} is a spatial weighting function quantifying the geographic proximity of farm j to farm i (e.g. the reciprocal of the square rooted distance between the farms); and N is the total number of farms in the sample. The spatial weight (w_{ij}) thus treats the probability of a neighbourhood infection as a decreasing function of the distance from an infected farm (Elbers *et al*, 1999). Q_{ikt} was calculated for each farm in the at-risk population for every day of the study period.

A Cumulative Distribution Function (CDF) was calculated for the daily values of the Q statistic (Q_{ikt}). The CDF describes the probability of a random variable being smaller than or equal to a specific value, and allowed us to quantify the distribution of

Q_{ikt} per region and per phase. We calculated CDF on a daily basis to evaluate and track exposure to infected and infectious farms (e.g. nearby farms in their TRW) through time.

In accordance with Mannelli *et al* (2007), the study period was divided into three phases, corresponding to the first and second quarters and the last half, to capture the initial spread and subsequent time course of HPAI in the two regions (Phase 1: December 5, 1999–January 3, 2000; Phase 2: January 4, 2000–February 1, 2000; Phase 3: February 2, 2000–April 5, 2000). A measure of spatial clustering of exposure for each farm over each phase was obtained by summing for each farm the daily values of Q statistic over the length of the phase considered (T) (equation 2). Large values of this statistic indicated farms with high exposure to the risk of infection by proximity.

$$Q_{ik} = \sum_{t=0}^T Q_{ikt} \quad (2)$$

Due to the different length of the study phases, the values of Q statistic at local level were re-scaled by dividing by the number of days during which birds were kept in the farm (flock-days):

$$Q_i^{ph} = \frac{Q_{ik}}{f_i} ; \quad (3)$$

where f_i is the number of flock-days for the i th farm. This allowed us to compare the phase-based Q statistic across farms in a manner that accounted for differences in flock size from farm to farm and through time.

The statistical significance of Q_i^{ph} was tested using a conditional Monte Carlo randomization with 99 replications. In each replication the infection status of the i th farm (that being considered in the analysis) was kept constant while the vector containing the $N-1$ infection status identifiers for the other farms was rearranged, and

the Q statistic was recalculated. For each farm, the distribution of simulated Q statistic values was compared with the observed, allowing us to assess whether the observed values were due to chance alone. With 99 replications we could resolve p -values as small as 0.01. The values of Q_i^{ph} were mapped for those farms that were significant at the 0.01 level using a classified colour scheme determined by the Jenks Classification Method (Jenks, 1967).

In order to evaluate the effects of region, phase of the epidemic, and outbreak occurrence, a new binary outcome (Q_bin) variable was created, taking value 1 if the farm i at time t was exposed to at least one infective nearest neighbour (i.e. $Q_{ikt} > 0$), and $Q_bin = 0$ otherwise. A generalised estimating equation (GEE), corresponding to a logistic regression (binomial error distribution, logit link), was subsequently implemented, taking into account correlation among Q_bin values that were obtained for the same premises on different days (exchangeable correlation structure) (Diggle *et al*, 2002). Model validation was accomplished by goodness-of-fit statistics (deviance and Pearson's χ^2) (Littell *et al*, 2002). In the model, Phase of the epidemics was coded by using phase 3 as the reference category, while Region was coded as Lombardy = 1 and Veneto = 0 (reference category).

2.3 Notes on data processing

The Q statistic, the Cumulative Distribution Function and the conditional Monte Carlo randomization were calculated using the R software version 2.8.0 (Ihaka and Gentleman, 1999; R Development Core Team, 2008), using the *stats*, *lattice* and *spdep* packages. ESRI® ArcMap™ 9.3 was used to map the significant Q_i^{ph} . The GEE model was implemented through PROC GENMOD in SAS® ver. 9.1.3 (SAS Institutes, 2004).

3. Results and discussion.

During the course of the HPAI epidemic exposure of susceptible poultry farms to IFs in the TRW was characterized by an increase from the first month of the epidemic (phase 1) to the second month (phase 2), followed by a reduction in the last half of the epidemic (phase 3), as indicated by the cumulative distribution of Q_{ikt} (Figure 3).

The overall proportion of farm population with a $Q_{ikt} > 0$ was greater in Lombardy, indicating that, in this region, a larger number of farms were exposed to at least one infective IF. Moreover, the reduction of the proportion of the farm-days with $Q_{ikt} > 0$ from phase 2 to phase 3 was more marked in Veneto than in Lombardy. The percentage of flock-days that were characterized by values of $Q_{ikt} > 0$ in the Lombardy region was 4.5% in phase 1, 14.4% in phase 2, and 7.0% in phase 3, whereas in Veneto, the percentage was 2.6% in phase 1, 7.3% in phase 2, and dropped to 1.4% in phase 3. In addition, the reduction of the maximum levels of Q_{ikt} from phase 2 to phase 3 (reported on the x-axes of the graphs in Figure 3) was greater in Veneto than in Lombardy, as shown by a more marked shift to the left of the cumulative distribution of Q_{ikt} in the two phases. In the GEE analysis (Table 1), both the reduction in the proportion of flock-days with $Q_{bin} = 1$ from phase 1 to phase 3, and from phase 2 to phase 3, was stronger in Veneto, as shown by the statistically significant interaction between region and phase (the negative sign of the interaction is due to the coding used for Region and Phase). The assumption of randomness of missing observations, which is required in GEE (Diggle *et al*, 2002), was not met in the case of poultry farms which were excluded from the data after HPAI occurrence or depopulation. Nevertheless, both exploratory analysis and the GEE results support the

conclusion of different time patterns of exposure to proximity to IFs in Lombardy and Veneto.

Within regions, in phase 1, significant Q_i^{ph} values were most frequent for farms in Lombardy, near the border with Veneto (Figure 4). In phase 2, significant Q_i^{ph} values were relatively dispersed through the study area, and although the highest Q_i^{ph} values were in Veneto, the majority of significant values were found in Lombardy (Figure 5). In phase 3, significant Q_i^{ph} values were mostly observed in the central part of Lombardy, as a consequence of the North-West spread of the infection. In Veneto Q_i^{ph} was generally low (Figure 6), indicating that only a few farms were significantly exposed to the risk of neighbourhood infection in the last phase of the epidemic.

The greatest levels of exposure to proximity to IFs for Lombardy poultry flocks were in agreement with the highest incidence rate of HPAI in this region, where most of the poultry production was concentrated in the area that was most severely affected by HPAI (Figure 1). Conversely, certain areas of Veneto, such as the hills in the province of Verona, were partially spared by the epidemic despite a high poultry population density. A negative association between altitude and the risk of HPAI was previously found in Veneto, but no plausible explanation is available for this observation (Mannelli et al, 2006).

The greater decrease of Q_{ikt} and Q_i^{ph} in Veneto, especially in the last phase of the epidemic, was associated with marked reductions in the at-risk population in this region, where, in phase 3, the poultry population was 56.3% of the population in phase 1. In Lombardy, the population was reduced to a lesser extent and, in phase 3, it still was 68.2% of its size in phase 1. Depopulation was carried out intensively in the area of Veneto that was more heavily affected by HPAI during the early phases of the epidemic, and was achieved by slaughter and a ban on restocking of IFs, and by the

pre-emptive slaughter of poultry on susceptible farms in the proximity of IFs (Figure 2).

A previous study showed that the effect of proximity to an IF (< 1500 m distance), as a risk factor for HPAI, did not change during the course of the epidemic in Italy (Mannelli et al, 2006). In this study the Q statistic allowed us to evaluate spatial and temporal changes in exposure as measured by the geographic proximity of susceptible to infected and infectious farms. HPAI transmission did occur among relatively distant farms, and proximity explained, at the most, 31.3% of the total risk at the population level (population attributable risk) (Mannelli et al, 2006). The HPAI's reproductive ratios (R_h ; the average number of new IFs that were caused by an infectious farm) was greater in phase 1 than in phase 2 (Mannelli et al, 2007), showing a different time pattern than that observed for Q_{ikt} . Such a difference can be explained by the fact that R_h was calculated without taking into account space and, therefore, including transmission among relatively distant farms. In contrast, distance was taken into account when calculating the Q statistic which is, therefore, ideally suited to evaluate the effects of control measures to reduce the risk of transmission among neighbouring farms, for example through pre-emptive slaughter based upon proximity to IFs.

In recent studies, HPAI transmission was evaluated by accounting for distance. This was accomplished by either considering the nearest IFs as the source of infection in the estimation of R_0 (Ward et al, 2007), or by introducing a transmission kernel modulating the probability of disease spread in space (Boender et al 2007, Dorigatti et al, 2010). However, R_0 cannot be directly compared the Q statistic since they measure two different things: R_0 measures the average number of new infections arising from an infected farm, while Q statistics assess proximity-based exposure of susceptible

farms to infected farms. As such R_0 and Q may be used in a complimentary fashion to better inform infection control and surveillance decisions. Different epidemiological techniques need to be applied to the analysis of epidemics of infectious diseases of livestock, to obtain different types of information from the available data and to focus on different characteristics of the epidemics. This study supplemented the analysis of HPAI reproductive ratios with Q statistic that provide spatially and temporally local measures of exposure risk. The combination of measures of transmission and of exposure may complement one another, and the integration and comparison of results from these techniques is required to draw sound conclusions from observational data, and to better guide the prevention and control of future epidemics.

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Conflict of interest statement

GMJ is president of BioMedware, a software firm that is conducting research on Q statistic with funding from the National Cancer Institute of the United States.

The other authors declare that they have no competing interests.

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Table 1. Results of the Generalized Estimating Equation model for the variable Q_bin , calculated from the 1999-2000 H7N1 Highly Pathogenic Avian Influenza epidemic in North-Eastern Italy.

Variable	Category	Observations (farm-days)	% $Q_bin^{(a)} > 0$	Parameter		
				Estimate	95% C.I.	<i>p</i> -value
Region	Lombardy	90519	8.23	1.31	1.08 ; 1.53	<.0001
	Veneto	134366	3.42	0.00	REF	REF
Phase	Phase 1	71725	3.34	-0.31	-0.54 ; -0.069	0.01
	Phase 2	61019	10.10	0.86	0.69 ; 1.03	<.0001
	Phase 3	92141	3.78	0.00	REF	REF
Health status	Infected	382 ^(b)	38.74 ^(b)	1.33	1.07 ; 1.59	<.0001
	Uninfected	224504	5.30	0.00	REF	REF
Phase1*Region	--	--	--	-0.65	-0.97 ; -0.34	<.0001
Phase2*Region	--	--	--	-0.48	-0.69 ; -0.26	<.0001

^(a) Q_bin is a variable that takes value 1 when $Q_{ikt} > 0$ (i.e. the farm i at time t is exposed to at least one infective nearest neighbour), and $Q_bin = 0$ otherwise.

^(b) Only the day of AI confirmation is included, so the number of farm-days is equal to the number of infected farms (IFs)

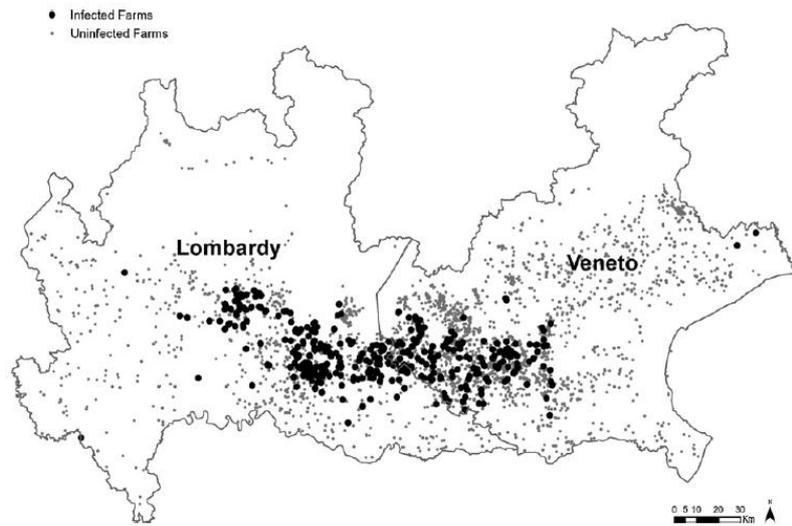


Fig. 1. Geographical distribution of infected and uninfected farms during the 1999–2000 H7N1 Highly Pathogenic Avian Influenza epidemic in North-Eastern Italy.

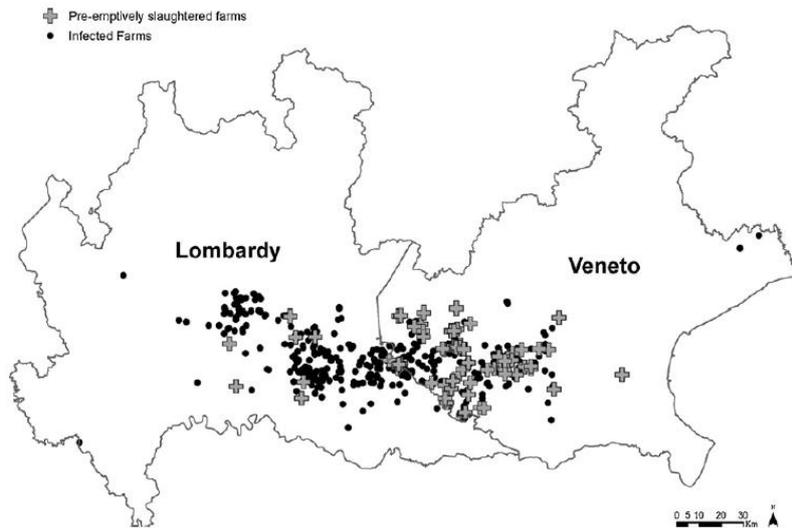


Fig. 2. Geographical location of pre-emptively slaughtered farms during the 1999–2000 H7N1 Highly Pathogenic Avian Influenza epidemic in North-Eastern Italy.

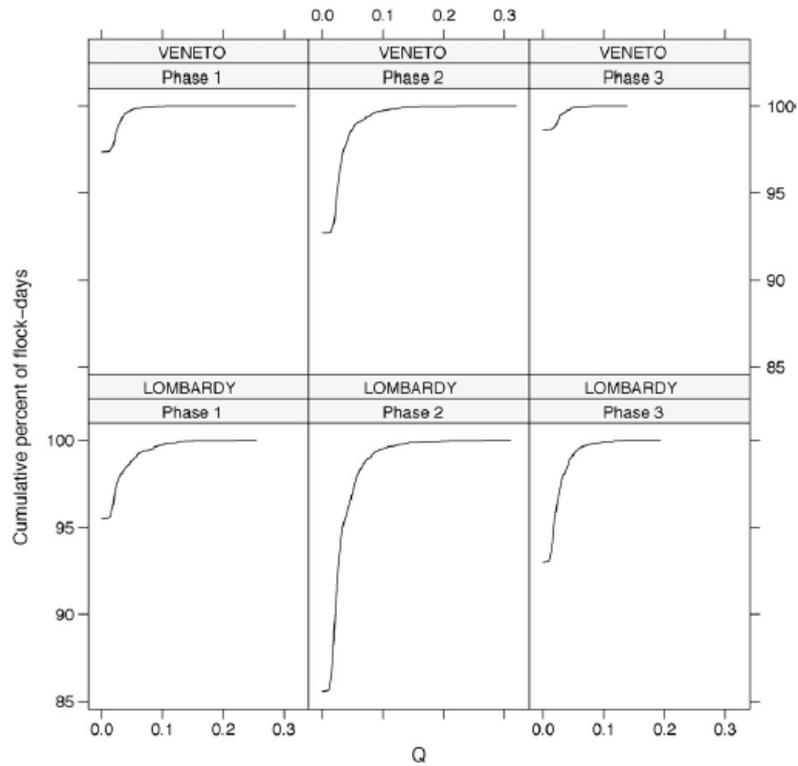


Fig. 3. Cumulative Distribution Function of Q in Veneto and Lombardy, in three phases of the 1999–2000 H7N1 Highly Pathogenic Avian Influenza epidemic in North-Eastern Italy.

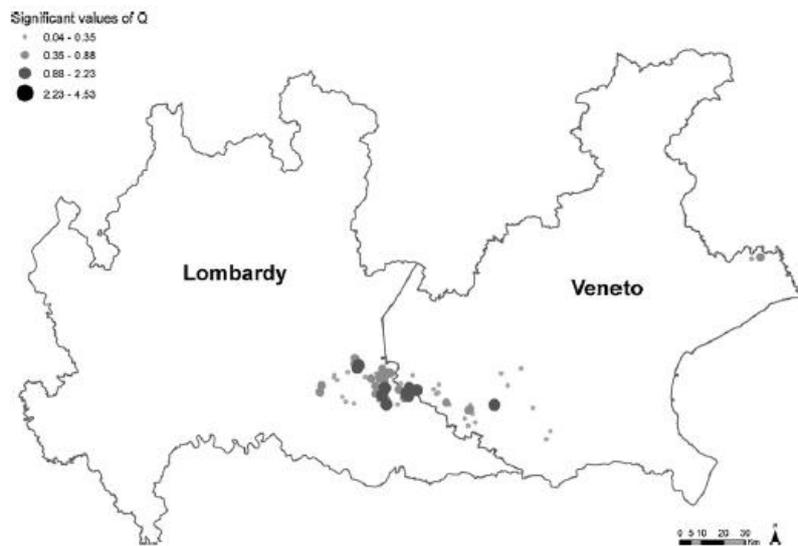


Fig. 4. Geographical location of significant Q_1^{ph} values detected during phase 1 of the 1999–2000 H7N1 Highly Pathogenic Avian Influenza epidemic in North-Eastern Italy. Values plotted are the calculated Q_1^{ph} values that had probabilities $p \leq 0.01$.

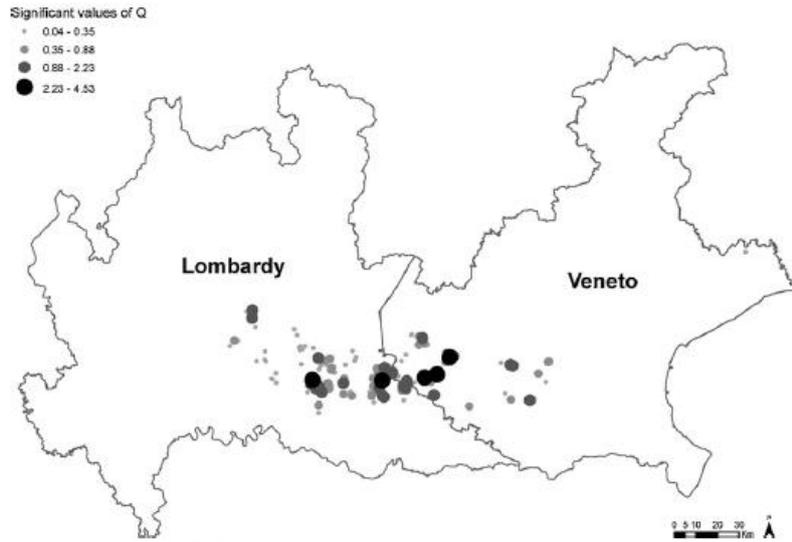


Fig. 5. Geographical location of significant Q_i^{ph} values detected during phase 2 of the 1999–2000 H7N1 Highly Pathogenic Avian Influenza epidemic in North-Eastern Italy. Values plotted are the calculated Q_i^{ph} values that had probabilities $p \leq 0.01$.

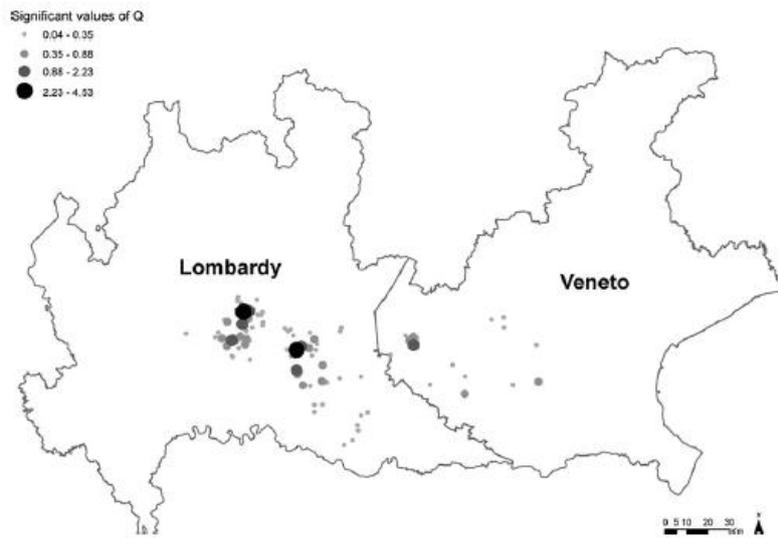


Fig. 6. Geographical location of significant Q_i^{ph} values detected during phase 3 of the 1999–2000 H7N1 Highly Pathogenic Avian Influenza epidemic in North-Eastern Italy. Values plotted are the calculated Q_i^{ph} values that had probabilities $p \leq 0.01$.