IDENTIFYING AREAS WITH A HIGH RISK OF HUMAN INFECTION WITH THE AVIAN INFLUENZA A (H7N9) VIRUS IN EAST ASIA

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Summary

Objectives—The rapid emergence, spread, and disease severity of avian influenza A(H7N9) in China has prompted concerns about a possible pandemic and regional spread in the coming months. The objective of this study was to predict the risk of future human infections with H7N9 in China and neighboring countries by assessing the association between H7N9 cases at sentinel hospitals and putative agricultural, climatic, and demographic risk factors.

Methods—This cross-sectional study used the locations of H7N9 cases and negative cases from China's influenza-like illness surveillance network. After identifying H7N9 risk factors with

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logistic regression, we used Geographic Information Systems (GIS) to construct predictive maps of H7N9 risk across Asia.

Results—Live bird market density was associated with human H7N9 infections reported in China from March-May 2013. Based on these cases, our model accurately predicted the virus' spread into Guangxi autonomous region in February 2014. Outside China, we find there is a high risk that the virus will spread to northern Vietnam, due to the import of poultry from China.

Conclusions—Our risk map can focus efforts to improve surveillance in poultry and humans, which may facilitate early identification and treatment of human cases.

Keywords

chickens; influenza in birds; influenza A virus – H7N9 subtype; international health problems; surveillance

Introduction

Avian influenza A (H7N9) virus has generated concern due to its rapid spread, high case fatality, virological factors that suggest adaption to mammalian hosts, lack of population immunity, and potential for person-to-person transmission. Within five months of the first reported case in eastern China in March 2013, the virus spread to the northern and southern parts of the country[1]. The fatality rate in 379 cases as of 3 March 2014 has been 30% with most patients presenting with symptoms of severe pneumonia[1, 2]. Although poultry exposure in live bird markets (LBMs) is the most significant risk factor for H7N9 infection in humans[3], the virus may transmit from person-to-person in very occasional cases when there is prolonged, unprotected contact with an index case[4]. H7N9 strains have also been reported to develop resistance in cases treated with oseltamivir, complicating treatment and leading to worse clinical outcomes[5, 6].

As of 3 March 2014, 82% of cases have occurred in eastern China (Shanghai and the neighboring provinces of Jiangsu and Zhejiang) and southern China (Guangdong province). However, in April and December 2013, two patients were hospitalized in Taiwan after being infected with H7N9 in Jiangsu[7, 8], and an additional patient was hospitalized in Malaysia in February 2014 following infection in Guangdong[9], highlighting the potential for long distance spread via air travel. After peaking in March and early April 2013, the number of new cases decreased significantly in late April and May following the closure of LBMs in the affected areas in early April and no cases were reported in June[10]. The sharp reduction in cases could be due to many reasons, including the fact that seasonal and avian influenza in humans historically reach low levels during the summer in China[11]. However, new cases were detected in in July, August, October–December 2013, and January–March 2014[1] raising the question of when and where human infections with H7N9 might occur next.

The objective of this paper is to predict the risk of future human infections with H7N9 in China and adjacent countries in East Asia. We did this by identifying agricultural, climatic, and demographic risk factors for current H7N9 infections in humans and constructing a regression model to predict future risk. The surveillance of H7N9 in poultry cannot rely on bird die-offs or illness of poultry since H7N9 infection in poultry is asymptomatic[12].

Therefore, a risk map is needed to most effectively target and conduct animal surveillance to prioritize areas where circulation and spread among poultry in farms and LBMs is most likely. Such a risk map will focus efforts to improve surveillance in poultry and humans, which may facilitate early identification and treatment of human cases as well as timely implementation of intervention measures.

Materials and methods

Surveillance for H7N9

We used a cross-sectional study design to identify putative risk factors for H7N9 infections in humans reported by surveillance between 4 March and 28 May 2013. We used cases reported from July to December to validate the model. The analysis was carried out at the scale of the county (*xian*), an administrative unit below the provincial level. County size reflects provincial history and politics[13]. Cities may contain several counties. For example, cities reporting H7N9 encompass 6.77 counties on average (Fig. A1).

To construct a map of the risk of H7N9 in each county in China, we first required positive H7N9 cases. We used the geographic location of positive H7N9 cases reported to the Chinese Center for Disease Control and Prevention (Fig. 1), and assigned cases to counties based on the six digit postal code of the patient's home. In addition, the model required the locations of negative cases. Due to surveillance bias, we could not assume that counties reporting no H7N9 had no human infections. For this reason, we utilized data from China's influenza-like illness (ILI) surveillance network[14], which tested individuals and found negatives. We classified a county as negative if all of the samples collected at hospitals in the county from March to May tested negative for H7N9. The logistic regression model described below was fitted to data from counties that reported H7N9 cases and counties that submitted samples to the ILI network and tested negative. Counties that did not submit samples to the ILI network (*n*=2012, which is 83% of China's counties) were not used to fit the model in the main text. In the Supplementary Material, we construct a model that assumes that counties reporting no cases were negative (Table A2, Fig. A2).

For each county in the surveillance data set, we calculated the value of four predictor variables hypothesized to be drivers of H7N9 infections in humans (Table A1 lists the data sources and A3 the median and quartile values among the counties).

LBM density—Most patients infected with H7N9 reported exposure to poultry at LBMs[3]; in addition, the prevalence of antibodies against H7N9 may be higher in LBM workers than in the general population[15]. H7N9 has been isolated from chickens in LBMs as well as ducks and pigeons[16]. We used data on market locations in 2012[17] to test whether LBM density predicted H7N9 in humans.

Temperature and relative humidity—Since cold, dry conditions increase the transmission of the influenza A virus in animal models[18], we hypothesized that counties with low temperatures and relative humidity would be more likely to have H7N9 infections in humans. Although absolute humidity is a more significant determinant of influenza

transmission efficiency than relative humidity[19], spatial data were only available for the latter.

Human population density—We hypothesized that high human population density could serve as a proxy for the intensity of poultry consumption, farming, or trading.

Distance from past H7N9 cases—Poultry farmers in China occasionally bypass nearby retail markets to sell to wholesale markets thousands of kilometers away[20, 21]. Large wholesale hubs such as those in Shanghai, Hunan province, and the Guangxi autonomous region supply retail markets where consumers purchase birds. As of 3 March 2014, H7N9 has been detected in birds and environmental samples at retail and wholesale markets but not farms[22]. A case-control study indicates that exposure to chickens at retail markets is the most risk important factor for H7N9 infection in humans[3]. We assume that a county close to a reported case has high exposure to H7N9 because the virus has entered the local retail market chain.

Logistic regression

All predictor variables except distance were included in a logistic regression to predict the occurrence of H7N9 infections in humans at the county scale. We utilized logistic regression because this approach has been used to quantify the risk of other zoonotic infections such as H5N1 avian influenza[23, 24]. The model included an offset term to account for the fact that sampling effort was greater in more populous counties. After fitting the regression model to the positive and negative counties in China (Fig. 1), we applied the model to counties in China that did not submit samples to the ILI network and to adjacent countries in Asia.

Combined risk model

The logistic regression predicts the risk of H7N9 infection in humans based on the counties' agricultural, climatic, and demographic characteristics. To account for the effect of geographic proximity on H7N9 risk, we calculated the distance along roads from each county in East Asia to the nearest county in China where H7N9 has been reported in humans. After creating a map of the risk of infected poultry movement and a map of the risk of H7N9 in humans based on agricultural, climatic, and demographic characteristics, we multiplied the maps by one another (Fig. 2). This provides a composite measure of risk that incorporates suitability for H7N9 based on environmental characteristics as well as exposure to H7N9 based on geographic proximity.

Results

Risk factors for H7N9 infections in humans in China (March–May 2013)

Of 2411 counties in China, 373 counties were negative for H7N9 and 56 were positive in our surveillance data set. The logistic regression model based on the surveillance data identified LBM density as the most significant risk factor (Table 1). The odds ratio for LBM density was 1.08, meaning that the risk of H7N9 infection in humans increases 8% for each additional LBM per km^2. Temperature also approached significance (p=0.056). When we assumed that counties reporting no H7N9 were negative, LBM density was highly

significant and temperature was slightly significant (Table A2). There was no relationship between H7N9 infections in humans and relative humidity or human population density (Table 1). We assessed the goodness of fit of the model via a Hosmer-Lemeshow test, in which the null hypothesis is that the logistic regression fits the data well[25]. We failed to reject the null hypothesis, indicating that our model explains a significant amount of variation in H7N9 risk (Hosmer-Lemeshow $\hat{C}$=8.89, df=8, p=0.35). However, we cannot rule out that other variables not considered here are important drivers of H7N9.

Accuracy assessment of the spatial model

To validate the logistic regression model, we first partitioned the surveillance data into a training set comprising 75% of the positive and 75% of the negative counties and tested the model's accuracy on the withheld 25%. The partitioning was done randomly and with replication (n=10,000). The model constructed from the training set had high predictive power when applied to the test set (AUC = 0.843, ROC contrast test chi-square = 1.15×10^5, $df = 1$, $p < .0001$). The model was constructed using human cases from March to May 2013. We further validated the model by assessing its ability to predict new human cases that occurred in Guangdong province in August-December, Hebei province in July, Jiangsu in December, and Zhejiang province in October-December that the model classified as having a high risk of human infection with H7N9. The predicted probability of H7N9 was 0.82 in Guangdong, 0.56 in Hebei, 0.89 in Jiangsu, and 0.94 in Zhejiang. The model constructed from cases reported between March and May 2013 predicts a high risk of H7N9 in the Guangxi autonomous region, which borders Guangdong (Fig. 3). As predicted, two human cases were reported in Guangxi in February 2014[26]. The model that classifies counties reporting no H7N9 as negative also predicts a hotspot in this region (Fig A2). In general, this model predicts fewer areas to have a high risk of H7N9 because the large number of counties assumed to be negative swamps the small number of positives.

Predicting future hotspots of H7N9 in East Asia

Outside China, the model predicts a high risk of H7N9 infections in humans in northern Vietnam. Guangdong, where H7N9 has been isolated from chickens and humans, is within 200 km of the Vietnamese border. Since our model does not include a time parameter, we cannot predict when future outbreaks might occur. Developing spatio-temporal predictions would several seasons of data[27], which is currently unavailable as H7N9 is an emerging infection. Other possible future sites of H7N9 outbreaks in Southeast Asia identified by the model include northern Laos and eastern Myanmar.

Discussion

Like the present study, Fang et al.[17] mapped the risk of H7N9 using the locations of human cases in China during the spring of 2013. The model presented here was developed in collaboration with Fang et al. but differed from the earlier model in several respects. First, the current model incorporates a county's proximity to reported cases as a predictor of the spread of H7N9. In addition, rather than using random negatives, the current model includes individuals who were tested during ILI surveillance and found to be negative (potential biases of ILI surveillance for detecting negatives are discussed below). Furthermore, the

current risk map was based on a logistic regression model that included an offset term to account for the fact that H7N9 surveillance was more intensive in populous areas. Finally, whereas the previous risk map covered China, the present risk map was constructed for China and neighboring countries in East Asia.

Since the two models were constructed from H7N9 infections in humans in the first half of 2013, how well did they predict cases in the second half of the year? Jiangsu and Zhejiang provinces reported cases in the spring of 2013 and have also reported new cases since June. In both provinces, the two models predicted a risk of future cases of 75% or greater. During the second half of 2013, Hebei and Guangdong provinces reported a total of eight cases but neither had reported cases in the spring. In these two provinces, both models predict some risk of H7N9. However, the magnitude of the risk predicted by the current model is higher (Hebei: 20% in Fang et al.[17] vs. 56% in present model; Guangdong: 40–60% in Fang et al. vs. 75–100% in this study). To this extent, the present model appears to provide somewhat more accurate predictions when validated on out-of-sample data. Our map was constructed using cases reported during the virus' initial emergence in eastern China from March-May 2013. However, the model accurately predicted the virus' spread into the Guangxi autonomous region in southern China, which occurred during the second wave of H7N9 infections (December 2013–February 2014).

Since our sampling design was cross-sectional, it is not possible to conclude that there is a causal relationship between H7N9 infections in humans in China and the variables that were significant in our statistical model. However, our results suggest hypotheses that should be tested more specifically in future studies. The significant association between LBM density and H7N9 cases in our model provides further support for the hypothesis that LBMs are an important source of H7N9 transmission to humans[3, 10, 28]. A previous study found a tight coupling between climatic variables and seasonal influenza in humans in Hong Kong[29]. We did not detect a significant relationship between H7N9 and climate, though temperature approached significance. This may reflect differences in transmission between seasonal and avian influenza. In the case of seasonal influenza, humidity affects the distance that virus particles travel[30]. However, given that H7N9 is a novel infection, we do not yet fully understand the routes of transmission and have not yet observed the impact of seasonality on its emergence.

Since most H7N9 cases have been reported in large cities, why was there no relationship between H7N9 and human population density according to our model? We found that the surveillance effort to detect H7N9 cases was much greater in densely populated cities (Spearman's rho = 0.35, $p = 2.71 \times 10^{-16}$). When the logistic regression model was adjusted to account for the intensity of sampling, there was no effect of population on the risk of H7N9 infection in humans. Our results suggest that LBM density, which was uncorrelated with population, is the most important risk factor among those analyzed here.

Controlling H7N9 in China will require multi-pronged policies involving the public health, food safety, and veterinary sectors. Closing LBMs appears to be an effective approach for eradicating or reducing H7N9 infections in humans[10]. In poultry, policies to control H7N9 include culling on positive farms and vaccination. Human vaccines against H7N9 are under

development[31, 32]. However, no H7N9 vaccine for poultry is currently available. Although vaccination of poultry against H5N1 is widespread in China, there may be little incentive for poultry producers to vaccinate against H7N9 due to its low pathogenicity in domestic birds and vaccine-induced antibodies may confuse surveillance efforts. Measures that have been effective for controlling other subtypes of avian influenza at LBMs in China include mandatory monthly rest days and bans on keeping live birds overnight[33]. These utility of these approaches for controlling H7N9 merits investigation.

Our results support strengthening LBM and human surveillance in northern Vietnam, whose poultry trade with China and proximity to sites where H7N9 has been detected in Guangdong and Guangxi make it the area outside China where the virus is most likely to spread next. In northern Vietnam, every day 100 tons of hens that are past their peak egg productivity called "spent hens" are imported from China into Quang Ninh and Lang Son, where they are sold at higher prices as meat chickens[34]. There is also considerable cross-border trade of day-old chicks and ducklings[35]. Poultry sellers routinely transport live birds long distances to wholesale markets within northern Vietnam[36], which could enable H7N9 to spread extensively if it is introduced. H5N1, which is endemic in Vietnamese poultry, is believed to have spread to Vietnam from China[37]. Other H7N9 hotspots predicted by the model in Southeast Asia include northern Laos and eastern Myanmar. However, these areas are not known to import chickens from provinces of China where H7N9 has been detected.

Among the limitations of this study was that our surveillance data were collected from patients who presented with ILI in urban areas rather than from individuals selected at random. The ILI surveillance system may have failed to detect H7N9 due to the biased age distribution of individuals sampled and geographic biases in screening. Concerning the first bias, although most H7N9 cases are 60 or older, only 7% of individuals screened by the ILI system were in this age group[14]. Concerning the second, H7N9 causes severe disease rather than subclinical infections[14, 38, 39], but the frequency of severe disease reporting varies across China[10]. For example, from March to May, the ILI system screened 100 samples per week from hospitals in northern China but 200 per week from hospitals in the rest of the country. In addition, since most sentinel hospitals are in urban areas, the surveillance network may have failed to detect H7N9 cases in rural populations. Due to geographic variation in testing efforts and age-biased sampling, the ILI surveillance system likely failed to detect cases of severe respiratory disease caused by H7N9. For instance, from March to May 2013, 8% of cases of pneumonia of unknown etiology (PUE) in China were confirmed to be H7N9[10]. In our data set, 37% of the negative counties were located in provinces that reported PUE. Thus, some of the putatively negative counties used to construct our risk map may have had cases of H7N9.

Due to these limitations of the surveillance data, our risk map may have low accuracy in northern China outside of areas with intensive H7N9 screening such as Beijing. The model appeared to perform well in Beijing to the extent that it classifies the municipality, which has reported five human cases of H7N9, as having a risk of 75–100% of H7N9 infections in humans. However, the Beijing CDC has had more aggressive surveillance and testing than some other parts of China, so the model had extensive training data for the city. Thus, the

performance of the model in Beijing likely reflects surveillance bias rather than the ability of the model to make accurate predictions when confronted with new data.

Future work should refine our risk map to account for genetic differences among strains of H7N9. In order to have sample size sufficiently large to construct a reliable logistic regression model, we conflated all strains of H7N9. However, some strains may be of more concern from a public health standpoint. For example, strains A/Anhui/1/2013 (H7N9) and A/Hangzhou/1/2013 (H7N9) carry residues at position 226 that allow them to bind to human respiratory cells, whereas the A/Shanghai/1/2013 (H7N9) strain lacks this specificity[6]. If H7N9 continues to be detected in humans, future research could identify areas where there is a high risk of human infection with strains that are adapted to human respiratory cells, or carry other mutations that affect human transmissibility, virulence, and sensitivity to antivirals. Another important area for future research is developing chicken density maps that cover all of Southeast Asia and distinguish between LBMs and farms, as the former have higher risk of H7N9 spillover to humans. The southern border of available chicken density maps is 18°N[40], which excludes Cambodia and southern Vietnam. Although a global map of poultry density is available from the UN Food & Agriculture Organization, it does not distinguish chickens from other domestic birds or LBMs from farms. Finally, validating our model in the field is an important task for future work, which could confirm the occurrence of H7N9 in predicted hotspots including northern Vietnam. If a large number of new H7N9 cases occurs, or if there are major changes in the input parameters of our regression model, such as the number of LBMs per county, the model could be rerun to provide updated predictions about the risk of infection in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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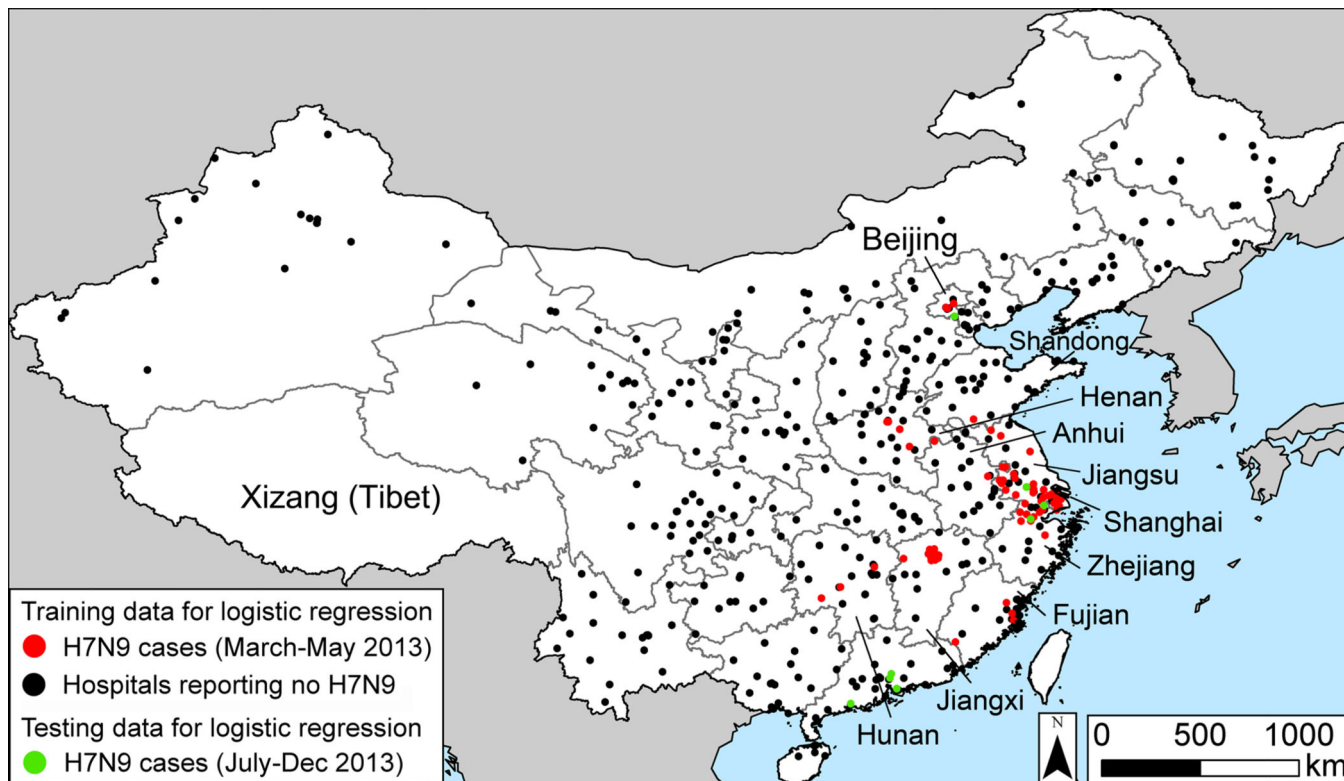
Fig. 1.
Geographic locations of influenza A (H7N9) infections in humans in China, March-May 2013. During this period, the samples were collected samples from all provinces except Xizang (Tibet).
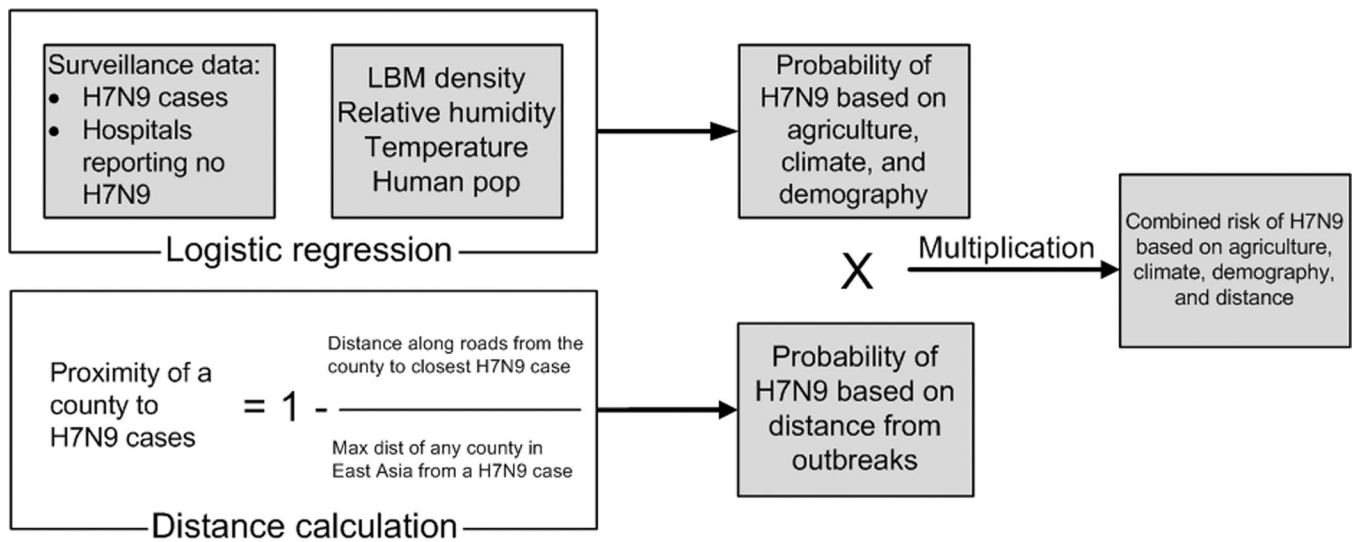
Fig. 2.
Calculation of a county's risk of H7N9 infection in humans based on agricultural, climatic, and demographic variables and distance from reported cases.
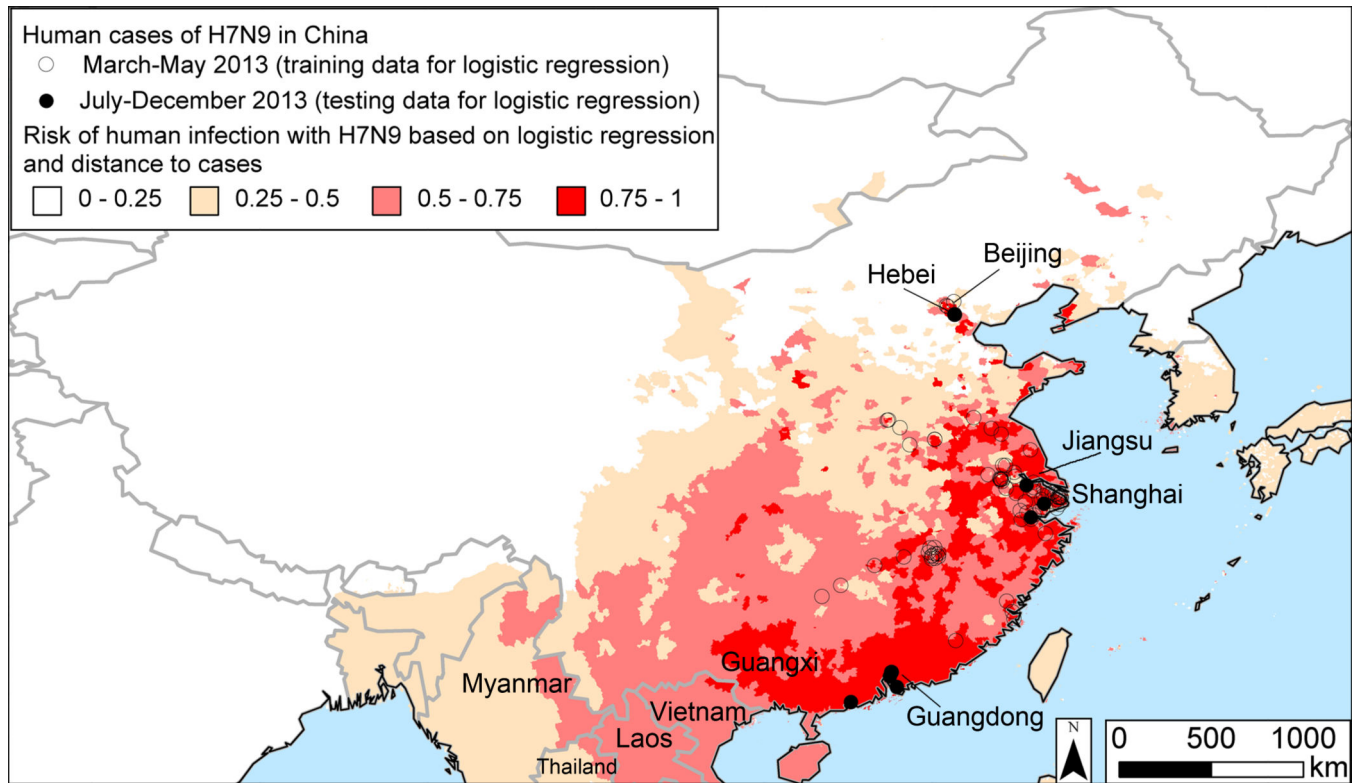
Fig. 3.
Future risk of H7N9 in East Asia based on cases reported in China from March-May 2013.

Table 1

Risk factors for H7N9 infections in humans based on surveillance data, March–May 2013.

Variable	Odds ratio (95% C.I.)	Coefficient	SE	p value
Intercept	Not applicable	−3.939	0.404	**<.0001**
LBM density (markets per km^2)	1.08 (1.04–1.12)	0.0733	0.0184	**<.0001**
Relative humidity (%)	0.99 (0.98–1.01)	-3.13×10^{-3}	7.1×10^{-3}	0.6595
Temperature (°C)	1.04 (0.99–1.08)	0.0378	0.0198	0.0563
Human population density (people per km^2)	1 (1–1)	4.5×10^{-5}	1.72×10^{-4}	0.7918