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A spatial analysis of the spread of mumps: the importance of college students and their spring-break-associated travel

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SUMMARY

To characterize the association between county-level risk factors and the incidence of mumps in the 2006 Iowa outbreak, we used generalized linear mixed models with the number of mumps cases per county as the dependent variable. To assess the impact of spring-break travel, we tested for differences in the proportions of mumps cases in three different age groups. In the final multivariable model, the proportion of Iowa's college students per county was positively associated ($P<0{\cdot}0001$) with mumps cases, but the number of colleges was negatively associated with cases ($P=0{\cdot}0002$). Thus, if the college students in a county were spread among more campuses, this was associated with fewer mumps cases. Finally, we found the proportion of mumps cases in both older and younger persons increased after 1 April ($P=0{\cdot}0029$), suggesting that spring-break college travel was associated with the spread of mumps to other age groups.

Key words: College students, spatial, travel, mumps, outbreaks.

INTRODUCTION

Mumps is an acute, systemic infection caused by a paramyxovirus. The most common clinical presentation consists of fever and parotitis. Less common manifestations include orchitis, encephalitis, pancreatitis and myocarditis [1, 2]. In most cases, the illness is self-limiting, and about one-third of people infected with the virus have a subclinical infection with either mild or no symptoms [3–5].

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The virus is transmitted via contact with infected droplets of saliva, respiratory secretions, or contaminated fomites [1]. There is strong epidemiological evidence that mumps can be transmitted prior to the development of symptoms and that the disease is most contagious just prior to the onset of parotitis [1]. There is also evidence that mumps can be transmitted by people with subclinical infections [1, 2, 4]. When symptoms occur, they typically occur about 18 days after exposure [1]. Following onset of symptoms, the virus can be cultured from the saliva of infected patients for up to 9 days [6, 7], but the proportion of patients shedding virus decreases rapidly after the onset of symptoms with about 11 % of patients shedding the virus in their saliva on day 5 [8].

Prior to the USA's introduction of the attenuated live vaccine against mumps in 1967, exposure to the disease and its acquisition were extremely common. In fact, most people born in the USA before 1957 are assumed by the public health community to have been infected. However, following the recommendation for the widespread use of mumps vaccine in the USA in 1979, the incidence of the disease decreased dramatically. For example, in the USA there were 152 209 cases in 1968 [9] compared to less than 300 cases in 2004 [10].

In early 2006, Iowa was the epicentre of the largest mumps outbreak in recent USA history. Although there were some cases in Iowa prior to January 2006, the epicentre for this outbreak occurred in Dubuque County, and several of the first documented cases occurred in college students in that county [10]. In fact, the majority of the cases during the Iowa outbreak, and the seven other highly affected contiguous states, occurred in young adults and teenagers. Over 80% of the college-age patients in this outbreak were attending college [11]. Thus, the age distribution of cases during this outbreak was unlike outbreaks in the pre-vaccination era, when most cases occurred in children under the age of 10 years [2, 4]. However, like the pre-vaccination era, most of the cases occurred in either late winter or early spring.

Why the epidemic started in Iowa is unclear, but it may have been introduced from a person travelling from the UK [12, 13], although there was no confirmed epidemiological link. What is also unclear is the predilection of the disease to patients in their late teens or early twenties. Although several cases were linked to college students and campuses, colleges in Iowa were not equally affected. For example, Black Hawk County reported 279 cases; the University of Northern Iowa is located in Black Hawk County and had a student enrolment of 12 513 in 2006. In contrast, Story County reported 13 cases; Iowa State University is located in Story County and had a student enrolment of 25 462. Furthermore, it was not clear if the disease preferentially affected young adults who just happened to be in college or young adults because they were in college. The purpose of this study was: (1) to describe county-level risk factors for the geographic spread of mumps, (2) to determine if there was a difference between the population of college students and the 'college-age' population in terms of their contribution to the propagation of the epidemic, (3) to determine the effect of college student travel during spring break on the spread of the disease.

MATERIALS AND METHODS

Statistical methods

To determine the county-level factors related to the spread of mumps across Iowa, we used generalized linear mixed models (GLMMs). Iowa occupies 55 000 square miles and is divided into 99 roughly equally sized and shaped counties. The number of mumps cases in each county served as the dependent variable. In formulating the GLMMs, the negative binomial distribution was assumed for the random component. (The negative binomial distribution is often used as an alternative to the Poisson distribution to model count data in the presence of over-dispersion.) The log link was employed to relate the expected number of mumps cases in the county to the systematic component, which represents potential county-level risk factors. An offset variable defined as the log of the county population size was incorporated in the systematic component to adjust for population differences. This GLMM formulation allows us to characterize the association between the expected proportion of mumps cases in a county and the county-level independent variables of interest.

We considered the following independent variables: the proportion of the county population aged 15–24 years, the number of colleges, the proportion of Iowa's college students attending college in the county, and the economic pull factor. The pull factor measures the amount of sales tax generated in a county from out-of-county customers and thus is a proxy for travel into a county from other counties.

To account for differences in risk due to spatial propagation, we computed the Euclidean distance, using latitude and longitude, from the centroid of each of the 99 counties in Iowa to the epicentre of the outbreak county (Dubuque County). We used these distances to define a categorical risk-zone variable at the county level. Thus, each county was assigned to a risk zone based upon its distance from the epicentre.

The county centroids (latitude and longitude) were also used in defining a suitable spatial covariance structure. Outcomes in nearby counties are probably correlated. Moreover, it is reasonable to assume that the strength of this correlation depends upon the distance between the locations at which the outcomes are collected. The isotropic power covariance structure

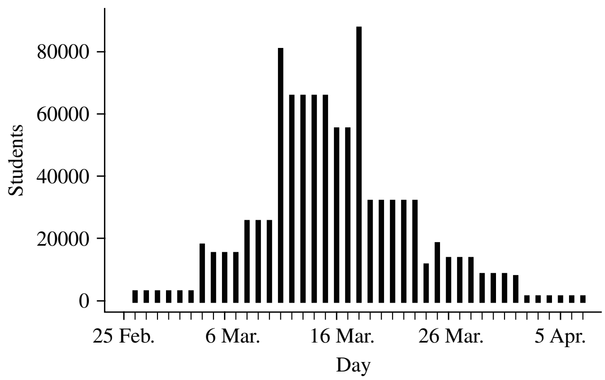

Fig. 1. Estimated number of Iowa college students on spring break by day.

used in our GLMMs implies that the correlation between outcomes in two counties decreases as the Euclidean distance between the counties increases.

Given the potential role that college students played in spreading mumps, and given that the majority of the cases occurred during the late winter and spring, we investigated the impact of the timing of college student spring-break-associated travel on mumps propagation. Using a χ^2 test, we tested the null hypothesis that the age of a case was independent of whether the case developed before or after the spring-break season. We considered two time periods: before and after 1 April 2006, and three age groups: college aged (17–23 years), and both younger (<17 years) and older (>23 years) than college aged. We chose 1 April because this date is 18 days after 14 March, the mean date for the distribution of Iowa college students on spring break (Fig. 1). Eighteen days were added to 14 March to adjust for the average incubation period of mumps [1].

Data sources

We obtained the number of cases per county and dates for each of the cases from the University Hygienic Laboratory (UHL) in Iowa City. The population for each county by age (in 5-year intervals) was based on US Census data and obtained from the Regional Capacity Analysis Program (ReCAP) at Iowa State University [14]. The number of colleges and proportion of Iowa college students in each county was computed from data provided by the Iowa College Student Aid Commission [15]. Economic pull factor is used for community trade analysis and is a measure of movement in counties for retail and consumption purposes. It is calculated by dividing the *per capita* retail sales for a particular county by the *per capita* sales for the state. The pull-factor data used in our analysis was generated by ReCAP at Iowa State University [14]. For the spring-break travel analysis, we define college age as being between the ages of 17 and 23 years, inclusive. The dates of spring break for each college were determined by contacting the colleges or by visiting individual college websites. All statistical analyses were performed using SAS version 9.1 (SAS Institute, USA). Specifically, the generalized linear mixed modelling was conducted using the SAS procedure GLIMMIX.

RESULTS

Figure 2 represents the total number of cases in each county and the rate of mumps cases for each county per 1000 population, and Figure 3 represents the number of colleges and proportion of Iowa college students per county. To adjust for geographic differences in risk resulting from the spatial propagation of the disease, we used a categorical variable that represents five county-level risk zones based on the distance from the epicentre of the outbreak. This categorical variable was chosen after formulating several different distance-based risk adjustment variables, both quantitative and qualitative. A generalized linear model was fitted using each candidate variable, and Akaike's Information Criterion (AIC) was employed to evaluate the fit. The final variable was selected based on the model that resulted in the minimum value of AIC. The levels of the resultant categorical variable are illustrated in Figure 4, with the epicentre (Dubuque County) comprising the first risk zone, the next three zones containing ten counties each, and the final risk zone including the remaining 68 counties.

Subsequent GLMMs were fitted using the risk-zone variable as a random effect in the systematic component, in conjunction with an isotropic spatial covariance structure. In modelling the expected incidence for a county, the incorporation of the random effect provides an adjustment based on the zone which contains the county, to allow for higher incidence in the higher risk zones. In the fitted GLMMs, the effect estimates for the five zones tend to decrease as expected, i.e. the estimates become progressively smaller as the proximity from the epicentre decreases. The overall GLMM correlation structure accommodates within-zone associations (via the isotropic spatial covariance function) as well as between-zone associations (via the risk zone random effect).

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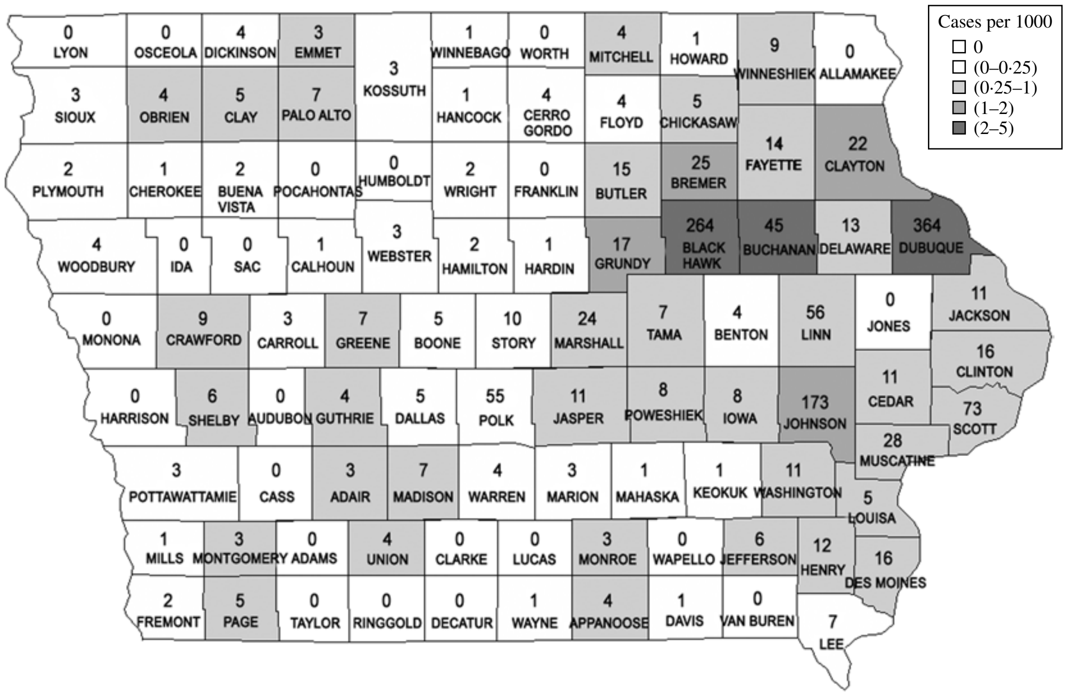

Fig. 2. County-level map of Iowa displaying number of cases and county rate per 1000 people.

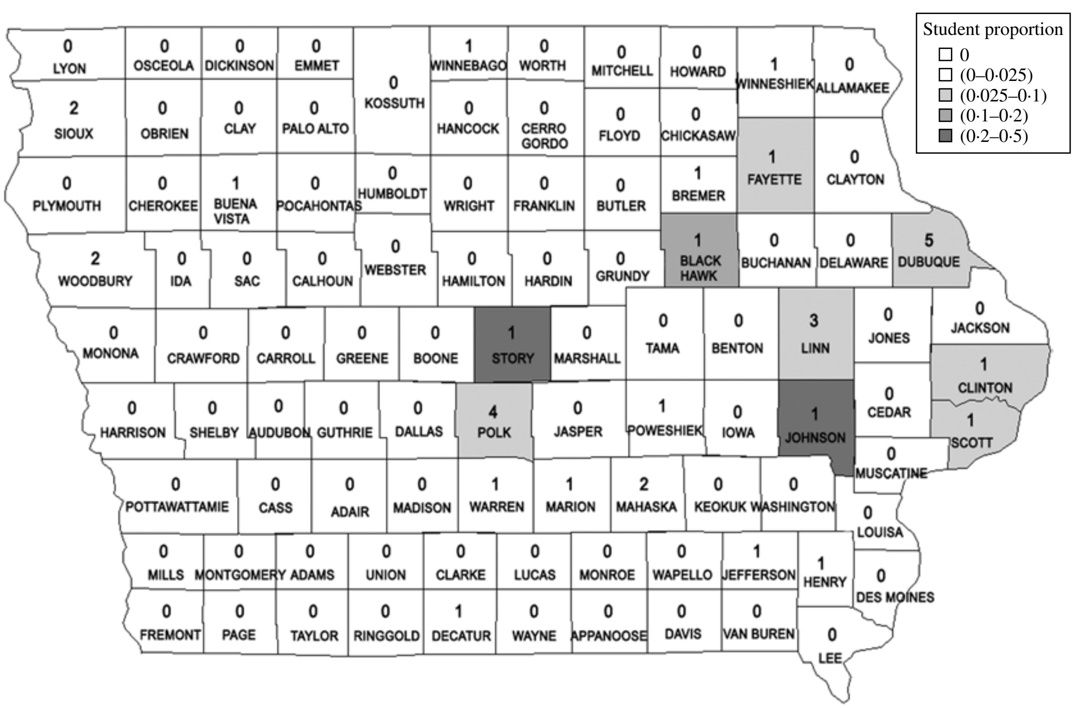

Fig. 3. Number of colleges and proportion of Iowa college students per county.

However, the between-zone associations were found to be negligible.

For the candidate risk factors of interest, GLMM univariable fixed-effect analysis revealed that the number of cases of mumps in each county, adjusted for county population size, was negatively associated with the number of colleges in each county, although the association was not significant at the 0·05 level ($P=0{\cdot}1749$, 95% CI $-0{\cdot}1986$ to $0{\cdot}0367$). The number of cases was positively associated with the proportion

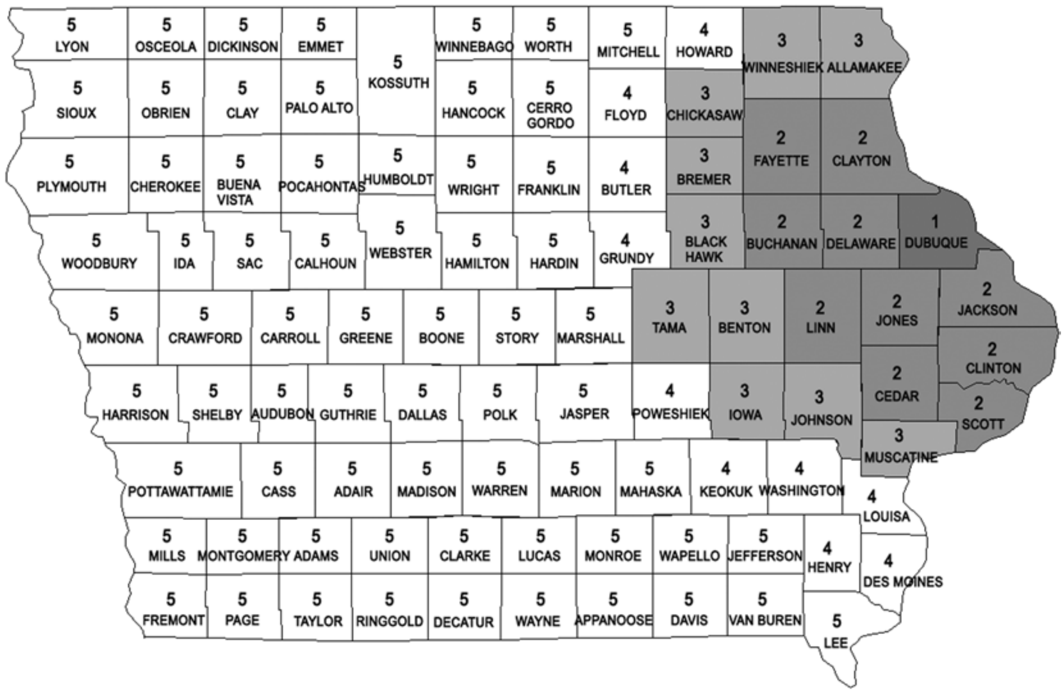

Fig. 4. Five distance strata representing five levels of the categorical risk-zone variable.

Table 1. *Results of final multivariable generalized linear mixed model*

Variable	Estimate	95% CI	*P* value
Number of colleges	−0·22	(−0·3298 to −0·1069)	0·0002
Proportion of Iowa college students	4·82	(2·5458 to 7·0940)	<0·0001

of Iowa college students in each county ($P=0{\cdot}0358$, 95% CI 0·2234–6·3667) and the proportion of county residents between the ages of 15 and 24 years ($P=0{\cdot}0050$, 95% CI 1·4873–8·1444). The association with the economic pull factor for each county was also positive, although not significant at the 0·05 level ($P=0{\cdot}3354$, 95% CI −0·1965 to 0·5705).

We considered each of the candidate variables for inclusion in a multivariable GLMM. For the final GLMM (Table 1), the number of colleges was negatively associated with mumps cases ($P=0{\cdot}0002$), and the proportion of Iowa's college students was positively associated with mumps cases ($P<0{\cdot}0001$). Based on a consideration of partial test *P* values and pseudo-AIC values for the fitted models, the variables representing the proportion of county residents between the ages of 15 and 24 years and pull factor were not retained in the final model. The results suggest that for a fixed number of colleges, within a particular risk stratum, the risk of disease increases as the proportion of college students increases. Additionally, for a fixed proportion of college students, within a specific risk stratum, the risk of disease decreases as the number of colleges increases.

To determine the impact of college-associated spring-break travel on the propagation of mumps, we considered the proportion of mumps cases in college-aged individuals, and individuals both older and younger than college age. We employed a χ^2 test to determine whether these proportions changed before and after 1 April 2006 (Table 2). The proportion of cases in older and younger people increased after 1 April, while the proportion of cases in college-aged people decreased accordingly after 1 April ($P=0{\cdot}0029$).

DISCUSSION

One of the most disconcerting aspects of this outbreak was that it occurred among a highly vaccinated population. Previous to this outbreak, the most recent large outbreak of mumps in the USA was attributed to suboptimal vaccine coverage [9]. A recent mumps outbreak in the UK in 2005 was also linked to suboptimal vaccination coverage [16]. However, the UK outbreak also raised questions about the effectiveness

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Table 2. *Number of mumps cases by age group stratified by date*

Age (yr)	Before 1 April 2006	1 April 2006 and after
<17	66 (19·6)	254 (21·9)
17–23	130 (38·6)	334 (28·8)
>23	141 (41·8)	571 (49·3)

Data are presented as number of cases (percentage of column total).

of the vaccine, as well as the possibility of waning immunity to mumps [17]. Certainly for the outbreak to occur, Iowa needed a susceptible population. Given the high level of vaccination in Iowa, waning immunity probably served as a prerequisite for the outbreak. However, we demonstrate that it was not the only factor. Our results suggest that the social environment of college students (i.e. their social networks) contributed to the spread of mumps during this outbreak.

Most recent outbreaks involve people in their late teens or early twenties. But it has not been clear if this is solely an age effect due to waning immunity or a combination of factors unique to that age group (e.g. going to college and living in dormitories). Our population-based analysis indicates the importance of the latter. Thus, it was not merely the population of young adults (all of whom should be at risk from waning immunity to mumps) but the proportion of Iowa college students that was significant in our final model. The results from our model suggest that it was the college students' social networks, reinforced by close-knit aspects of college living that potentiated the spread of mumps in Iowa. This result is consistent with historical observations. Close living and working conditions have long been associated with mumps outbreaks. For example, as early as the first half of the nineteenth century, mumps outbreaks were noted to have a 'predilection for prisons, orphanages, boarding schools, garrisons and ships' [1]. Although primary students are also often in close quarters, college students share more similarities to the garrisons and boarding schools that were often implicated in outbreaks in the pre-vaccination era. For example, unlike primary students, college students tend to eat more meals together, study together after class, live in crowded dormitories, and attend larger lecture halls.

Another indication that college students' social networks played an important role was that in our final model, if the proportion of Iowa college students in a county was divided between more colleges (i.e. there were more colleges in a county controlling for proportion of Iowa students in the county), this was protective against mumps in that county. In other words, if the college students in a county were partitioned into smaller networks (more college campuses), this was associated with fewer mumps cases.

Finally, the association of an increase in the proportion of cases among older and younger people following a short period of high mobility in college students during the spring break supports our hypothesis that social networks played an important role in the spread of mumps in Iowa. If it were simply waning immunity that contributed to this outbreak, we would not expect that the proportion of cases in the younger age group would have increased after the college spring-break period.

Since the introduction of the vaccine, the average age of mumps cases has increased [9]. Currently, the average age seems to match that of college students. In fact, since the Iowa outbreak, there have been other outbreaks and most of these involved college campuses. For example, in October 2006 an outbreak occurred at Wheaton College in Illinois [18], and mumps spread during 2007 on several different college campuses in Canada [19]. The continuation of the spread of mumps indicates that the disease will be problematic in the future. In the USA, the Advisory Committee on Immunization Practices now recommends documentation of two mumps vaccinations for all students at post-high-school educational institutions [20]. However, given that a high percentage of people in the Iowa outbreak had two doses of the vaccine, other infection control measures need to be considered. Extremely strict contact isolation for symptomatic students helped to limit the spread of the outbreak to less than 100 cases during the Wheaton College outbreak. But for such measures to be effective, cases need to be identified quickly.

The recent outbreaks of mumps in college students, in conjunction with our results, suggest a need for an increased awareness of mumps on college campuses. Given that 43% of nations do not vaccinate against mumps [21], future importation of mumps is highly likely and continued vigilance is necessary in countries that do vaccinate against mumps. Prior to the 2006 outbreak, mumps was considered a relatively unlikely cause of parotitis in a highly vaccinated population [22]. In fact, some of the first mumps cases in Iowa were in students presenting with parotitis and positive antibody (IgM) tests. However, they were thought by some not to have mumps given that they had previously been vaccinated. For example, in December 2005, the Iowa Department of Public Health, in one of its weekly epidemiology updates discussing multiple reports of clusters of parotitis in young persons stated 'individuals who have had two doses of mumps vaccine who are ill with mumps-like symptoms and/or parotitis are NOT likely to be ill due to mumps' [23]. In the future, regardless of mumps vaccination status, mumps should be in the differential diagnosis of parotitis. Moreover, a single case of mumps presenting in a student should trigger heightened surveillance for additional cases and prompt notification of public health officials.

There are limitations to our study. First, we did not use individual-level data. For example, we did not consider (or know) specific travel patterns for individual cases. Although such data would have been ideal, for outbreak investigations these data are often missing or incomplete and are relatively expensive to collect. Furthermore, there are significant privacy considerations. Because of these common limitations, one of our goals was to show that a spatial analysis using readily available county-level data can be helpful for understanding and explaining the spread of infectious disease outbreaks. Second, there were specific limitations to the county-level data that we used: although we knew the age of cases, at the county-level age was only available at 5-year intervals. Thus, we were only able to approximate the proportion of 'college age' people in a county (e.g. 15–24 years). Finally, we would have liked to include data about vaccination coverage in each county in our analysis, but due to the disparate nature of healthcare payments in the USA, these data are neither collected nor reported in a uniform and widespread fashion.

The county-level analysis in the study was made possible by using a GLMM framework to account for the spatial covariance between observations (i.e. numbers of mumps cases in different counties). Obviously the number of mumps cases in one county is expected to be correlated with the number of cases in an adjacent county, and this correlation is likely to persist even after the adjustment of key explanatory effects. In studying the geographic spread of infectious diseases, accommodating spatial correlation necessitates the use of more advanced models than traditional generalized linear models. The GLMM framework allowed us to take advantage of available county-level data, and to use these data to help explain the spread of the outbreak. With the availability of statistical software to fit such models (such as the GLIMMIX procedure in SAS), we hope that this modeling framework will become more accessible and will be used to study other outbreaks in a similar fashion.

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DECLARATION OF INTEREST

None.

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