Are People Living Near Modern Swine Production Facilities at Increased Risk of Influenza Virus Infection?

Paul M. Lantos,1 Kate Hoffman,1 Michael Höhle,2 Benjamin Anderson,1 and Gregory C. Gray1

1Duke University, Durham, North Carolina; and 2Stockholm University, Sweden

**Background.** Swine can harbor influenza viruses that are pathogenic to humans. Previous studies support an increased risk of human influenza cases among individuals with swine contact. North Carolina has the second-largest swine industry in the United States.

**Methods.** We investigated the spatiotemporal association between influenza-like illnesses (ILIs) and licensed swine operations from 2008 to 2012 in North Carolina. We determined the week in which ILI cases peaked and statistically estimated their week of onset. This was performed for all 100 North Carolina counties for 4 consecutive influenza seasons. We used linear models to correlate the number of permitted swine operations per county with the weeks of onset and peak ILI activity.

**Results.** We found that during the 2009–2010 and 2010–2011 influenza seasons, both seasons in which the pandemic 2009 H1N1 influenza A virus circulated, ILI peaked earlier in counties with a higher number of licensed swine operations. We did not observe this in 2008–2009 or 2011–2012, nor did we observe a relationship between ILI onset week and number of swine operations.

**Conclusions.** Our findings suggest that concentrated swine feeding operations amplified transmission of influenza during years in which H1N1 was circulating. This has implications for vaccine strategies targeting swine workers, as well as virologic surveillance in areas with large concentrations of swine.

**Keywords.** influenza; H1N1; zoonosis; pigs; epidemiology.

North Carolina’s pig farming industry, with nearly 10 million pigs, is second only to Iowa in annual pig sales, comprising 14.5% of the US market [1]. As pigs may be infected with numerous strains of influenza viruses and large production farms are often home to multiple influenza virus strains, modern swine production facilities may serve as generators of novel swine-like influenza viruses [2–9]. Additionally, modern swine production practices may inadvertently disseminate these viruses to numerous other farms as pigs and equipment are moved about production networks [10,11]. In the United States, several subtypes of influenza A virus (H1N1, H1N2, and H3N2), have classically circulated in pigs [3, 8, 12–14]. The introduction and broad dissemination of human pandemic 2009 H1N1 has increased the variety of influenza A virus strains circulating in pigs, resulting in further novel virus production and human infections with novel swine-like “variant” strains [7, 8, 15–19]. Consequently, pigs serve as a potential source for influenza A virus to infect livestock workers and, given their transmissibility, the families and communities with whom the workers live [19]. Assuming that some human and swine influenza viruses may move freely between species, and that modern pig farms may serve as an amplifying influenza virus reservoir, we hypothesized that there exist spatiotemporal associations of seasonal human influenza infections in North Carolina. In this report, we document our spatiotemporal analysis of influenza-like illnesses (ILIs) using geographic information system (GIS) software.

**METHODS**

This study was approved by the Duke University Institutional Review Board and received ethical clearance from the North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT) surveillance program.

**Data Sources**

The NC DETECT program collects weekly ILI case counts from emergency departments throughout North Carolina. We obtained these data, tabulated by county, of patient residence for the calendar years 2008–2012. These cases were defined by the NC DETECT case definition (Supplementary Data 1) [6]. We obtained a table of licensed swine feeding operations from the North Carolina Division of Water Resources, with 2328 permits active as of 5 January 2015 [15]. This table contained latitude and longitude coordinates for each permit, allowing it to be displayed as a point layer in GIS (Figure 1). The table also contained estimated head counts of swine at each permitted site. A spatial joining operation was performed to count the number of individual operations within each North Carolina county as well as the total number of swine. The number of...
swine per permitted site ranged from 12 to 63,450 (median, 3200 [interquartile range, 1975–5200]). The number of permitted sites and number of swine per county were closely correlated. Because head counts of live animals are much more likely to vary over time, we chose to use swine permits per county in our statistical models.

Data Preparation
We prepared a weekly count of ILI cases for each county from July 2008 to June 2012. The datasets were organized in yearly increments beginning with surveillance week 27 and ending with week 26 of the following calendar year. Week 27 corresponded roughly to early July. This was done to ensure that the peak activity of a single influenza season was not divided by the end of a calendar year. We analyzed each of the 4 July–June influenza years independently.

Data Analysis
All analyses were performed using the 100 counties of North Carolina as our unit of spatial analysis. We used ArcGIS 10.3.1 (ESRI, Redlands, California) for GIS processes, including preparation of map figures, and we used SAS 9.4 (SAS, Cary, North Carolina) and R 3.2.3 (www.r-project.org) for statistical analyses.

ILI cases occurred throughout the year due to nonspecificity of the case definition. There was a notable spike in cases, however, during the annual influenza epidemics. We examined 2 parameters to characterize the timing of the annual influenza epidemics during the 4 study years: the week in which ILI cases peaked for each county, and the week in which cases rose above their baseline. The onset week was estimated by fitting a negative binomial regression model using log-link and containing population offset, intercept, and a triangular function parameterized by onset week, peak location, and fade-out week, as well as the amplitude of the peak. This is a parametric model that detects an initial monotonic increase in events over a constant baseline.

We next statistically examined each of the 4 influenza seasons to determine whether there were spatiotemporal associations between ILI week of onset or peak and swine operations. This analysis was performed using multivariable robust regression models [20, 21]. The number of swine operations per county was highly skewed; many counties had no permitted facilities, but 2 counties had >450. As a consequence, to address potential nonlinearity of the covariate, a categorical variable was created for the number of operations: none (n = 38), 1–9 (n = 33), 10–24 (n = 12), 24–75 (n = 11), and >75 (n = 6). Although onset and peak week were approximately normally distributed, there was a small number of low-population counties in which ILIs peaked in an unlikely week for a particular influenza season (e.g., peaking in July). Analyses were restricted to counties in which the ILI onset or peak was within 3 standard deviations of the mean week across North Carolina in that year (maximum of 4 counties excluded in any analysis). We anticipated that associations between swine operations and flu onset could be confounded by population density or age of the population in each county and adjusted analyses for these factors. We performed additional analyses to identify relationships between ILI timing and other agriculture-associated variables, including crop acreage, hay acreage, and number of farms.

RESULTS
During the 4 influenza seasons studied, there was a total of 741,276 documented ILI cases across North Carolina: 178,228 in 2008–2009, 231,042 in 2009–2010, 183,894 in 2010–2011, and 148,112 in 2011–2012. Figure 2 illustrates the total statewide ILI counts per week for each of the influenza seasons. The 4 graphs begin in July and end the following June so that influenza seasons fall in the middle of each graph. A baseline of roughly 2000 ILI cases per week was observed during summer months. Peak ILI cases occurred in February of each year except during the pandemic H1N1 season in 2009–2010 in which a narrow peak occurred in September and early October 2009.
On visual inspection, we did not observe spatial associations between swine farm locations and the timing of ILI case onset (Figure 3). During the 2009–2010 season, 81% of counties had an onset detected within the month of July 2009. The onset weeks were widely dispersed over many months in the other 3 study years. There was no statistical association between week of ILI onset and number of licensed swine farm sites (Figure 4).

We did, by contrast, find spatiotemporal associations of swine farm locations and the timing of ILI cases peaking during years when a swine influenza virus freely moved between pigs and humans. In both the 2009–2010 and 2010–2011 seasons, ILI cases peaked earlier in the eastern NC counties near a denser concentration of swine operations. In both the 2009–2010 and the 2010–2011 seasons, both years in which H1N1 circulated widely, there was a statistically significant inverse association between week of ILI case peaking and number of licensed swine operations (Figure 4). For example, in 2009–2010, ILI peaked 2.78 weeks earlier in counties with >75 permitted operations than in counties with none (95% confidence interval, −4.46 to −1.10; P = .001; see Figure 4 for additional effect estimates). In the 2008–2009 flu season, the year prior to the first emergence of pandemic H1N1, ILI peaked later in counties with more permitted swine operations.

**DISCUSSION**

We have found a significant relationship between the peaking of ILI cases and the abundance of swine operations. This phenomenon was observed primarily during the 2009–2010 and 2010–2011 influenza seasons, years in which swine-associated H1N1 influenza was circulating.

This pattern was not observed during 2008–2009 or 2011–2012, years in which swine-derived influenza viruses were not as prevalent in human populations. In fact, in 2008–2009 the opposite phenomenon was observed, with ILI cases peaking later in counties with more swine permits. We hypothesize that this finding was not related to swine per se, but rather that other phenomena (such as high population density in non-agricultural counties) may have been a more important driver of the disease dynamic.

Consistent with our previously reported modeling data and observational data in Canada, our findings support the hypothesis that pigs may serve as an amplifying reservoir for influenza viruses that freely move across species [4, 19]. Abundant data now show that exposure to live pigs, either occupationally or at agricultural fairs, is a risk factor for human infection with swine influenza viruses. A heightened risk of zoonotic influenza among swine-exposed workers has now been demonstrated in Romania, the United States, and China [17, 22, 23]. Pandemic H1N1 virus infection was more common among swine industry workers in the United Kingdom than in the general population [16]. Spouses of swine industry workers, even with no animal exposure themselves, have had significantly increased seroreactivity to swine influenza viruses [5]. Communities with a large proportion of swine industry workers may experience a higher...
volume of influenza cases, and in themselves constitute a site of epidemic amplification [19].

Our study has several limitations. First, whereas during epidemics a high proportion of ILI cases is likely due to influenza A virus infection, ILI may also be caused by infection with numerous other respiratory viruses. This produces a substantial background noise that is quantitatively most important in counties with lower human populations (which had lower peak case counts). This clearly affected our onset analysis, in which the range of onset weeks exceeded the plausible influenza transmission season.

Figure 3. Spatiotemporal variation of influenza-like illness (ILI) over 4 influenza seasons, 2008–2009 to 2011–2012. Onset week was determined by statistically identifying an increase in cases over baseline. Peak week was that in which the highest number of ILI cases was reported. The color scale has a shade for each week, with a darker shade representing earlier week of peak or onset. In 2009–2010 and 2010–2011, peak week appears to be occurring earlier in southeast North Carolina, near the heaviest concentration of swine sites.
Second, our spatial analysis was limited by the county-level resolution of the case data. Neither the human populations nor their ILI events were evenly distributed within a given county, nor was their geographic proximity to swine operations. Moreover, swine industry farms were also not evenly distributed within counties; persons may have exposure to swine operations in a neighboring county, for instance. Farm size, by contrast, is unlikely to explain spatial or temporal variation in ILI cases. The average permitted farm had thousands of pigs, and the vast majority of permitted sites, regardless of size, were located in the same counties. We did not, at any rate, have access to case data at a fine enough spatial resolution (such as individual case data or zip codes) to test associations with sub-county level variability in farm size. Finally, we did not have a synonymous data source showing whether the distribution of swine permits changed during the study year. This is unlikely to have influenced the outcome of our study, as the counties where the swine industry is concentrated have not changed over time.

It is worth considering that the swine sites were merely markers of unmeasured factors that more directly influenced the timing of ILI peaking in those counties. It is unlikely, however, that these were mere markers of rural or agricultural counties. Many of the 100 counties in North Carolina are rural, and we did not find significant association with low population density, crop acreage, or number of farms. Thus, we believe that, among the variables we had available, swine were a more plausible explanation for the ILI timing.

Our study adds to a growing body of evidence that live swine may be a crucible for human influenza epidemics. This highlights the importance of enhanced biosurveillance among livestock and livestock workers, both to identify putative epidemic virus strains and to infer when nearby human communities may be at increased risk. Moreover, this justifies increased efforts to achieve universal influenza vaccination among swine workers and others within their communities.

**Supplementary Data**

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.
Notes

Acknowledgments. The case data used in this study were provided by North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT), an advanced, statewide public health surveillance system. NC DETECT is funded with federal funds by the North Carolina Division of Public Health (NC DPH), Public Health Emergency Preparedness Grant, and managed through a collaboration between NC DPH and the University of North Carolina at Chapel Hill Department of Emergency Medicine’s Carolina Center for Health Informatics. The NC DETECT Data Oversight Committee includes representatives from the NC DPH, UNC NC DETECT Team, and North Carolina Hospital Association.


Disclaimer. The funding source (National Institutes of Health [NIH] and Duke Clinical and Translational Science Award) funded professional efforts devoted to this project, but there was no involvement of the funding source in design, execution, or presentation of this study. The NC DETECT Data Oversight Committee does not take responsibility for the scientific validity or accuracy of methodology, results, statistical analyses, or conclusions presented.

Financial support. P. M. L. was supported by the National Center for Advancing Translational Sciences of the NIH (award number KL2 TR001115). M. H. was supported by the Swedish Research Council (grant number 2015-05182). G. C. G. was supported in part by the NIH/National Institute of Allergy and Infectious Diseases (R01AI108993-01A1 to G. C. G.).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References