Published in final edited form as:

Health Place. 2010 November ; 16(6): 1230–1239. doi:10.1016/j.healthplace.2010.08.010.

Utilizing spatiotemporal analysis of influenza-like illness and rapid tests to focus swine-origin influenza virus intervention

J. Gaines Wilson^{1, *}, Jessica Ballou², Chris Yan², Susan P. Fisher-Hoch², Belinda Reininger², Jennifer Gay², Jennifer Salinas², Pablo Sanchez², Yvette Salinas³, Fidel Calvillo³, Leonel Lopez³, Ionara P. deLima⁴, and Joseph B. McCormick²

¹Dept. of Chemistry and Environmental Sciences; The University of Texas – Brownsville

²The University of Texas Health Science Center at Houston, School of Public Health - Brownsville campus

³Cameron County Department of Health and Human Services

⁴Ambiotech Engineering Group

Abstract

In the spring of 2009, a novel strain of H1N1 swine-origin influenza A virus (S-OIV) emerged in Mexico and the United States, and soon after was declared a pandemic by the World Health Organization. This work examined the ability of real-time reports of influenza-like illness (ILI) symptoms and rapid influenza diagnostic tests (RIDTs) to approximate the spatiotemporal distribution of PCR-confirmed S-OIV cases for the purposes of focusing local intervention efforts. Cluster and age-adjusted relative risk patterns of ILI, RIDT and S-OIV were assessed at a fine spatial scale at different time and space extents within Cameron County, Texas on the U.S.-Mexico border. Space-time patterns of ILI and RIDT were found to effectively characterize the areas with highest geographical risk of S-OIV within the first two weeks of the outbreak. Based on these results, ILI and/or RIDT may prove to be acceptable indicators of the location of S-OIV hotspots. Given that S-OIV data is often difficult to obtain real-time during an outbreak, these findings may be of use to public health officials targeting prevention and response efforts during future flu outbreaks.

Keywords

cluster; H1N1; swine flu; ILI; RIDT; GIS

INTRODUCTION

In April 2009, a strain of novel H1N1 swine-origin influenza A virus (S-OIV) emerged in Central Mexico and the United States and was soon after declared a pandemic by the World Health Organization (Dawood et al. 2009; Fraser et al. 2009). By July 2009, the WHO was reporting 94,512 laboratory confirmed cases and 429 deaths worldwide (Organization 2009). The limited studies on S-OIV to date have largely focused on global/macro-scale analyses (Fraser et al. 2009), historical/comparative analyses relative to the 1918 Spanish flu and other pandemics (Fraser et al. 2009; Morens et al. 2009; Zimmer and Burke 2009) and phylogenetic analyses (Morens et al. 2009; Nava et al. 2009; Smith et al. 2009). Several

*Correspondence to: Jeff Wilson, PhD Department of Chemistry and Environmental Sciences 80 Fort Brown – MO1.114 The University of Texas at Brownsville Brownsville, Texas 78520 phone: 956.882.6646 fax: 956.882.6702 jeff.wilson@utb.edu.

critical research questions remain unanswered. First, there have been few studies outlining the spatial distribution of the disease at the community scale. Understanding the nature of the spatiotemporal patterns of S-OIVs at the local level will be critical in designing intervention and community outreach programs for future influenza outbreaks. Second, there has been little work examining the extent to which data on more easily diagnosed conditions like influenza may inform researchers and public health officials of the distribution in time and space of S-OIV cases (Ginocchio et al. 2009; Vasoo et al. 2009). During the pandemic of spring of 2009, there were few S-OIV tests available and extended lag times between the swab and the actual confirmed results. Tests often had to be routed through several levels of public health agencies (local, county, state and federal) before the results were returned to local public health officials, a process taking approximately six weeks locally, and results were often not available until the outbreak had retreated or was over. No work to date has focused on evaluating the ability of other, more cost-effective and time-efficient measures to spatially predict local clusters and patterns of disease for S-OIVs. Evaluation and comparison of these more convenient measures may also make it possible to identify the highest risk geographic areas at an early stage of an outbreak, rather than performing analysis after the outbreak has subsided. This temporal aspect has also not been explored to date. If more accessible measures could accurately reflect S-OIV patterns early on in an outbreak, our ability to respond in a timely and effective manner (Cohen 2009) would be greatly improved, potentially mitigating the impacts of the disease and/or saving lives.

Our study takes place in Cameron County, Texas, which is located directly on the U.S.-Mexico border at the mouth of the Rio Grande River on the Gulf of Mexico (Fig. 1), an area known as the Lower Rio Grande Valley (LRGV). Brownsville is the closest point of entry by land into the United States from the likely origin of the S-OIV pandemic: the central Mexican town of La Gloria, Veracruz, which lies approximately 450 miles due south of Brownsville (Fig. 1) (Fraser et al. 2009). The local population is approximately 91% Hispanic (mostly of Mexican-American origin) and Cameron County is consistently ranked as among the most economically deprived counties in the entire United States (United States Census Bureau 2003). Median per-capita income in Cameron County was estimated at \$11,958 in 2006 with 32.1% of families below the poverty level, compared with 9.8% nationally (United States Census Bureau 2007). The population is known to have exceptionally poor health, even relative to other communities with similar demographics (Fisher-Hoch et al. 2010). Cameron County also has four busy international crossing points and an appreciable amount of cross-border population mixing is present daily. In March 2009 alone, 258,796 vehicles, 205,582 pedestrians and 13,192 commercial trucks crossed into the U.S. from Matamoros, Mexico and into Brownsville, the largest city in the County (Texas Center for Border Economic and Enterprise Development 2009).

This paper aims to accomplish several objectives, namely: (i) to characterize the spatiotemporal nature of the S-OIV outbreak at a fine spatial scale within a U.S.-Mexico border community; (ii) to systematically evaluate the effectiveness of ILI and RIDT in estimating the spatiotemporal nature of S-OIV cases at various time periods during the evolution of an outbreak; and (iii) comment on the suitability of utilizing ILI and RIDTs as surveillance measures to inform real-time outbreak surveillance in the absence of confirmed S-OIV results.

MATERIALS and METHODS

Case Definitions and Data Collection

The disease data in this study consists of three measures of influenza: ILI, RIDT, and S-OIV. The CDC defines Influenza-like-illness (ILI) as fever (temperature of 100°F [37.8°C] or greater) and a cough and/or a sore throat in the absence of a known cause other than

influenza (CDC 2009a). RIDT represents a case of Influenza A or B that has been confirmed by a rapid test, generally conducted on-site in a clinic, physician office, or hospital. Results of the test are immediately available. Finally, S-OIV indicates a laboratory-confirmed case of novel influenza A (H1N1) virus infection, defined by the CDC as illness in any person who had a respiratory specimen that tested positive for novel influenza A (H1N1) by rRT-PCR (CDC 2009a). The majority of S-OIV cases internationally have been persons experiencing influenza-like illness with relatively mild effects (CDC 2009a) and ILI diagnoses have been shown to be strongly linked to contact with the earliest treated S-OIV positive cases in Mexico (Perez-Padilla et al. 2009).

ILI cases were recorded (per CDC definition) by hospitals and clinics throughout Cameron County as patients arrived, and for a portion of these cases, additional data was collected through official investigations conducted by the Cameron County Department of Health and Human Services (CCDHHS). RIDT cases were collected through these follow-up investigations. Confirmed S-OIV cases were recorded by Texas Department of State Health Services (DSHS) laboratories in Austin and San Antonio, following confirmatory testing of any ILI patient samples that were sent in from any Texas hospital or clinic (all confirmed S-OIV cases were initially ILI cases). Reports of ILI were faxed from healthcare providers to the Cameron County Department of Health and Human Services at the beginning of each day during the outbreak and reached a total of 1563 reports by May 13th, 2009. These reports were classified as ILI for this analysis. Initial ILI reports contained the patient's home address, age, a date of report, and a date of onset, although date of onset was missing in approximately half (53%) of all reports. Investigations of these reports by CCDHHS staff ensued, consisting of a medical chart review and telephone questionnaire—this continued until June 5th, at which point, the DSHS issued instructions to discontinue investigations. Of the 1563 ILI cases, a total of 498 cases (22.5%) were investigated. The medical chart review revealed that 405 of the 498 (81.3%) investigated cases had a positive influenza A RIDT result. These cases were classified as RIDT in this analysis. ILI patient respiratory samples collected by healthcare providers (clinics and hospitals) were sent directly to DSHS testing facilities (Austin and San Antonio) for rRT-PCR (polymerase chain reaction)-confirmatory testing. Due to the backlog in laboratory testing, results for 378 Cameron County cases sampled as early as 26 April were not received at CCDHHS until June 30th. The rRT-PCR-confirmed cases were classified as S-OIV in this analysis. rRT-PCR testing continued on ILI patient samples also until June 5th, when DSHS issued instructions to limit testing only to samples from hospitalized patients. All reports and investigation files were compiled at CCDHHS and cases were reconciled and cleaned by UTSPH personnel using SAS v. 9.1 (SAS 2009). The full study time window for this study was from 26 April to 13 May. This range is appropriate, as CCDHHS did not initiate its reporting protocols with local hospitals and clinics until 26 April; ILI and RIDT reports were at their pre-outbreak baseline as of the end of the second week in May.

Spatiotemporal Analyses

All geographical analyses were based on the U.S. Census Bureau's 2000 census data aggregated to the smallest geographical unit at which full census data is available: the census block group (CBG). We utilized a Geographic Information System (GIS) to geocode all cases containing local, U.S. residential address data. Geocoding is the process of digitally referencing the geographic coordinates of a specific real-world location or area into a GIS. By geocoding the home addresses (from the DSHS Swine Influenza Case Report Form) from each set of data (ILI, RIDT, S-OIV), we were able to couple the disease data to U.S. census demographic data and establish rates at the CBG level. In 2000, our full study area of Cameron County had a total population of 335,227 in 232 census block groups with an average of 1,445 persons per CBG. Brownsville contained 158,371 persons in 117 census

block groups for a mean of 1,354 per CBG. Given the novelty of the H1N1 S-OIV, all persons were assumed to be at-risk for developing influenza illness. To calculate rates of illness, we aggregated all cases within a census block group over the time period of interest, and then divided by the total U.S. census population within the respective CBG. All spatial analyses were performed with ArcGIS v. 9.3 (ESRI 2009).

Cluster analyses were performed with SaTScan (Kulldorff 2009), a statistical tool for cluster detection and spatial analysis of the distribution of disease that has been used in a variety of health outcomes, including outbreaks of infectious diseases (Fischer et al. 2008; Kulldorff et al. 2005; Kulldorff et al. 2007; Oeltmann et al. 2008; Pearl et al. 2006). SaTScan imposes a circular scanning window on the map and varies the radius continuously from zero to 50% (the recommended window for maximum detection) to include different sets of neighboring census block groups (Kulldorff 1997). SaTScan evaluates the statistical significance of a possible cluster within each population window by examining the likelihood ratio, which is maximized over all the windows to identify the most likely disease cluster (Kulldorff 2009). SaTScan requires three files for input: a case file, a population file, and a geographic file. The case files were exported from the GIS and included age and respective date information for each case. As a fixed point of reference for comparing locations of cluster centers, a bearing and distance from the Cameron County Courthouse (LAT 25.908, LON -97.492) was set (see Fig. 1).

Influenza rates are known to be highly stratified by age in influenza pandemics (Simonsen et al. 1998). During the spring 2009 pandemic, the median age of patients with S-OIV infections in the U.S. and Europe was initially reported as 20–25 years and was later lowered to 13 years in the U.S. (Chowell et al. 2009; Fraser et al. 2009; Kelly et al. 2009). Accordingly, the ages in this analysis were classified into the following five categories along census breaks: (0–4; 5–9; 10–19; 20–49; and 50+). The population file was age-stratified into the five age categories, and the geographic file consisted of LAT and LON coordinates for the geographic centroids of each CBG. SaTScan adjusts for covariates and in this analysis we accounted for the age of the case relative to the categorical age distribution of the population (Kulldorff 2009). SaTScan outputs include information on the most likely cluster's center, radius and statistical significance. In addition, SaTScan also estimates the relative risk (RR) in each census block group of the health outcome under study after adjusting for covariates. These age-adjusted relative risks were then exported to the GIS with the adjusted relative risk calculated by SaTScan and joined to the appropriate CBG. For the study area under consideration, we first ran all cluster analyses considering data for the entire county, and then ran the tests for Brownsville CBGs only. Brownsville is the largest urban area in Cameron County and we wanted to consider clusters *within* Brownsville without bias from outlying areas. We ran both space-only cluster analyses as well as space-time for ILI, RIDT, and S-OIV.

The space-time cluster analysis option identifies not only the center and radius of a primary cluster, but also specifies a time window for when the cluster of new cases was present. For this type of analysis a time component is necessary. For ILI, the date of onset of symptoms was often not available, so we used the date that the report was received at the CCDHHS central data center. For the 53% of reports that did contain date of symptom onset, the difference between the date of symptom onset and the date the report was received averaged 3 days (± 2.9). All RIDT cases had date of symptom onset available from either the medical record or via the telephone questionnaire, so this was used for analysis. Date of sample collection was used for S-OIV analyses in the cluster model.

A total of 30 cluster analyses were performed using variations of data sets suited for particular disease measures, geographical extents and time periods. The first 12 tests

consisted of the three case types (ILI, RIDT, S-OIV) $\times$ two study area sizes (Cameron County or Brownsville) $\times$ two space-time options (space-only or space-time). The additional 18 runs consisted of space-time cluster analyses of all three measures in Brownsville and Cameron County split into four cumulative time periods (all starting at 26 April) so that we could examine changes in the cluster locations and RRs as the outbreak evolved. Period A was 26 April – 29 April; Period B included 26 April - 03 May, and Period C was from 26 April – 07 May, and the full period was 26 April – 13 May. These dates were chosen to account for the 13 workdays between April 26 and May 13. Because CCDHHS and many physicians remained open on Saturday, May 2, the time periods April 26–29 (A); April 30–May 3 (B); May 4–May 7 (C); and May 8– May 14(D) had 3, 3, 4, and 4 days of active surveillance, respectively. By examining the cumulative available data as the outbreak progressed and comparing it to the final analysis of the entire data set for ILI, RIDT and S-OIV, this design allowed us to pinpoint more accurately at which point in the outbreak it may be suitable to best assess the location of the cluster center and radius as well as the rates that are to be expected for the full outbreak period.

Due to inconsistencies in the types of dates (date of report, date of onset, date of sampling) available for ILI, RIDT, and S-OIV data sets, we were forced to use differing measures of time for each case. As the purpose of this study was to compare space-time patterns of ILI and RIDT to S-OIV, we chose as a starting point 26 April, when the Texas Department of State Health Services issued protocol for collecting specimens to be analyzed. For ILI, where date of report was used, this did not likely bias our space-time analysis as a comparison of the available data shows that the median date of illness onset was only two days earlier (May 2 versus May 4) than the median date detected using the date the report was received. For RIDT, we chose to use date of onset as it was available for 95% of this subset. Data for S-OIV date of onset were only available for 73%, while date of sampling was available for 97%—thus for this dataset, we used date of sampling. State laboratories became inundated with samples during the peak of the outbreak, and thus had to limit the number of samples to be tested. As such, the total number of confirmed S-OIV cases reported during this time period was likely an underestimate, as has been reported in other studies. Due to limited resources and time constraints, only 498 of all ILI reports could be investigated by CCDHHS before DSHS issued instructions to stop.

Finally, we performed several tests to evaluate the relationship between clusters detected using ILI and S-OIV and RIDT and S-OIV reports. For both the entire time period, and the three cumulative sub-periods, we calculated Pearson correlation coefficients for either ILI or RIDT relative to the rates in respective CBGs for S-OIV. We also determined the correlation between the RR of each measure (e.g. ILI or RIDT) and the corresponding S-OIV RR for each census block group.

RESULTS

For the study period from 26 April – 13 May there were a total of 1,563 reports of ILI recorded by CCDHHS. 1,247 (79.8%) of these were successfully geocoded, of which 969 were located in the Brownsville CBGs. Of the 405 RIDT positives with dates of onset during the study period, 321 were geocoded (79.3%) and 246 of these fell within Brownsville. There were 377 confirmed cases of S-OIV with report dates (one case was missing a report date) during the study period and 206 (55%) of these were geocoded; 151 S-OIV cases were located in Brownsville. Approximately 6% of the ILI and RIDT addresses and approximately 12% of the S-OIV addresses were P.O. Boxes. The remaining addresses were missing or not locatable either within the GIS or by using Google Maps. Most of the growth in new cases was between period A (26 April-29) and period B (26 April-03 May)

with ILI reports at the county level growing 192% (192 to 560), S-OIV from 138 to 208 (51%) and S-OIV from 57 to 108 (89%).

Figure 2 (a–c) shows the date distribution of ILI (2a), RIDT (2b), and S-OIV (2c) cases, by date of report, date of onset, and date of sampling, respectively. Each set is grouped into the same four time periods defined in the methods section. The large drops in the ILI distribution curve (02 May–03 and 09 May–10) reflect weekend dates in which hospitals and clinics did not fax reports to CCDHHS. Mondays following the weekends (04 May and 11 May) showed a spike in reports due to the backlog of reports that were not sent in over the weekend. The peak of the outbreak based on date of onset (RIDT) was registered on April 27, which coincides with the steep decline in new cases for all three measures between the second (B) and final sub-period (D) in our study. ILI and S-OIV curves show later peaks because the date of report and date of sampling typically lagged behind the date of onset by 2–3 days (patients were rarely reported or sampled on the day the first symptoms appeared). However, the general trend remains consistent across all three measures, with the peak of the epidemic coinciding with the end of April.

Space-Time Distribution of ILI, RIDT and S-OIV

Raw (non age-adjusted) incidence rates were calculated and plotted by quintile for all 232 CBGs in Cameron County based on geocoded data for ILI, RIDT, and S-OIV (Fig 3 a–f) and using the 2000 Census for each CBG as the population denominator. Rates ranged from 0 to 4,814 per 100,000 for ILI; from 0 to 963 for RIDT and 0 to 474 for SOIV. The distribution for all three measures, both in terms of rates and point addresses, appears to be denser in urban areas (Fig. 1) and most variable in the Brownsville area relative to other regions of the county (Fig. 3). When examining the distribution of points, the highest concentration of cases appears to be in the southeast and along Rio Grande River in Brownsville, the area closest to the border with Mexico, with a gap between the border and the main point concentrations for all three measures. While this pattern is most apparent with ILI (Fig. 3 b), it is also apparent with RIDT (Fig. 3 d) and less so with S-OIV (Fig. 3 f). Rates were plotted by quintile because the rate scales are not consistent across measures. The 4th and 5th (highest two quintiles) for all three measures were found in the outermost areas of the city and the area southeast of the Cameron County courthouse.

For the entire study period 26 April – 13 May, a total of 12 space and space-time clusters were performed for the Cameron County and Brownsville extents (Table 1). All clusters detected were significant to the 0.001 level except for the space-only cluster for Brownsville S-OIV ($p = 0.057$). For clusters taking into account all CBGs in Cameron County, cluster locations were consistent. All clusters for Cameron County were located in a Northeast to Easterly direction from the courthouse (from 51° to 77°). ILI and RIDT had the same cluster centers with identical radii, while S-OIV clusters for the space and space-time tests were centered S/SE of the ILI and RIDT cluster centers at a distance of 6.6 and 8.2 km from the courthouse and with radii of 6.6 and 7.7 km, respectively. The relative risk of clusters ranged from 3.1 for S-OIV space-only to 7.4 for the RIDT space-time test. All clusters overlapped in time from April 28 to May 3 (6 days). The ILI space-time cluster most accurately resembled the S-OIV space-time cluster for the County (at the city level, RIDT was closer on some measures), in location, RR estimation and time window of the cluster.

When the cluster analysis was restricted to the 119 Brownsville census block groups, ILI and RIDT again were similar with the exception of the ILI space-only cluster, which was located south and east of the other RIDT and ILI tests. The cluster centers ranged from 2.96 km to 10.3 km from the courthouse, and the radii ranged from 0 (i.e., the cluster was contained entirely within one CBG) to 8.8 km in diameter (incorporating multiple CBGs). Relative risks ranged from 1.9 for S-OIV space-only to a RR of 7.0 for the space-only ILI

cluster test. In Brownsville, the ILI space-time test most accurately reflected the location, the duration, and the relative risk of the S-OIV space-time clusters. For Brownsville, the temporal overlap for all clusters was two days less than the County extent, ranging from 29 April – 02 May (4 days).

Fig. 4 displays the spatiotemporal age-adjusted relative risks, cluster centers and cluster boundaries for ILI, RIDT and S-OIV with standardized categories of risk for cross-comparison for the Brownsville extent. There were higher RRs along the northern and eastern edges of the metropolitan area for ILI and RIDT, while higher S-OIV RRs were elevated in the south and southeast as well as the far north of the city. The relative risks within the ILI cluster area were mostly lower than 1.5, while RIDT and S-OIV had higher relative risks. The cluster center for ILI was 5.2 km east of the Courthouse, while the RIDT and S-OIV clusters were further east, at distances of 9.5 and 10.3 km, respectively. All clusters covered a relatively consistent area of the eastern and central-eastern parts of the city.

In order to understand the spatiotemporal nature and cluster shifts of cases for the entire outbreak period (26 April – 13 May), we performed a series of 18 additional cluster tests over progressive time periods (Table 2). All 18 tests resulted in significant clusters ($p < 0.001$). The first test consisted of the full date range 26 April – 13 May. We compared this 'standard' to the clusters utilizing data from 26 April to three end dates: (i) 29 April; (ii) 03 May; and (iii) 07 May. The change in distance, radius and relative risk relative to the full study period was tracked at the three time periods mid-outbreak. For the County extent, ILI in the second period most accurately reflected the full study period in location of the cluster, while the third period (to May 7) most accurately reflected the RR of the full period cluster, though it underestimated the RR by almost 20%. For RIDT and S-OIV, the third period (to 07 May) most accurately reflected the location and RR of the full-period cluster. For the Brownsville extent cluster analysis, ILI and RIDT measures did not accurately reflect their respective full-period clusters until the third period. However, the location, radius and relative risk of the S-OIV cluster for second period (03 May) matched the cluster for the full period (to 13 May).

Comparison of Measures

Utilizing the same time periods outlined above for raw rates and age-adjusted relative risks, we performed Pearson correlation tests to highlight the strength of the relationships between ILI and RIDT to S-OIV at each time point during the outbreak (Table 3). All correlations were significant to the 0.01 level. Pearson correlation coefficients between ILI and S-OIV rates (per 100,000) ranged from 0.334 for to 0.670. For every time period and for both extents (County and Brownsville), ILI was most strongly correlated with rates of S-OIV relative to RIDT. It is interesting to note that, at both the County and Brownsville extent, the highest correlation between rates of ILI and S-OIV was in the third period with a slight decline when utilizing full-period data. Correlates between RIDT and S-OIV full period age-adjusted relative risks and rates were highest in the in the fourth, full period ending 13 May.

DISCUSSION

This retrospective study presents the first known results characterizing patterns of several influenza disease measures (ILI, RIDT, and S-OIV) at a fine scale within a community during the spring 2009 novel 2009 H1N1 influenza pandemic. The key message of this work, in the broader sense, is that space-time patterns of ILI, RIDT and S-OIV can detect and similarly reflect the highest geographical risk areas early in an outbreak. Further, these three measures, which range in complexity and lead times of acquisition and processing, are similar and significantly correlated. Not only do age-adjusted relative risk and raw

population rate patterns appear to be closely aligned for the three measures, but the centers and extents of clusters as well as the temporal windows of the clusters were also largely in agreement. Therefore, it is reasonable to suggest that ILI and/or RIDT data, which are more easily acquired at the community level, could be used real-time during an outbreak rather than waiting weeks or months for laboratory PCR-confirmation of S-OIV. We also have shown that it may be possible to identify areas where intervention efforts may most effectively be focused in real-time during an outbreak, rather than relying on retrospective analyses of delayed reports.

As would be expected, the cases for all three measures consistently show more density in the urban area, but of particular interest is the finding of higher densities of points tracking northwest along the US-Mexico border with decreasing density moving away from the Rio Grande, especially in Brownsville (Figs. 3 b, d and f). To date, several studies have examined the effects of inter- (Colizza et al. 2007) and intra- national travel on the spread of influenza, including the spread of seasonal flu, (Brownstein et al. 2006; Crepey and Barthelemy 2007), avian flu (Guan et al. 2004) and very early work on the 2009 S-OIV (Fraser et al. 2009; Khan et al. 2009), there has been little work focused on space-time tracking of the outbreak in international border areas that experience high levels of cross-border population mixing on a daily basis. We have no data to support causal link between border crossings and influx of influenza, but this was not a focus of this study. This study supports future examinations of the effects of close proximity to the border. While the border was perhaps a means of introducing the virus, community demographics likely played a greater role in the establishment of disease. We were not able to determine the connections that each case had with relatives of business in Mexico, either through hospital records or personal interviews. The need for collection of this data was expressed to the surveillance team at the State level and we recommend that a network of shared statistics and crossing information should be set up between Brownsville and Matamoros.

Independent of population distribution, there does not appear to be any local clustering of case points associated with the three border crossing points in Brownsville. In all three measures, we also observed a band of concentration starting from approximately 5 km southeast of the County courthouse and stretching to a distance of ~10 km from the courthouse. It should be noted that the raw population rates in this same area were also in the highest quintile for all three measures. This area, known locally as 'Southmost', is in the lowest quartile of income and education, a factor which may influence healthcare access (van Doorslaer et al. 2006) and the likelihood that preventive services will be recommended by physicians (Solberg et al. 1997). These findings suggest that community demographics may play a greater role in the geographic distribution of disease, but this study supports future examinations of the role that our close proximity to an international border crossing played in the transmission of disease. In the future, it would be advantageous to enhance information sharing between U.S. and Mexican healthcare authorities for comparative evaluations.

Our full-period cluster results (Table 1 and shaded area only of Table 2) for the entire outbreak period (26 April – 13 May) indicate that there was strong agreement between ILI and RIDT in both cluster centers and radii at the County extent. Age-adjusted relative risks for the clusters were generally lower for S-OIV, possibly a reflection of under-reporting bias. At the Brownsville extent, the centers were mostly consistent for ILI and RIDT, with S-OIV clusters showing more variability. Cluster centers for all three measures in Brownsville were in the eastern or southeastern parts of the city and were of similar size (Fig. 3). The Southmost area, centered approximately 7 km S/SE of the courthouse, was included in all clusters, although it was near the cluster center for only the ILI test. While our cumulative time-sequenced testing of comparisons between ILI and S-OIV and RIDT

and S-OIV showed a better and earlier coincidence with ILI for the entire Brownsville extent, a visual examination of relative risks *within* the cluster boundaries suggest that RIDT more accurately portrays the pattern. ILI relative risk patterns do not appear to capture the distribution of S-OIV risk as well as RIDT.

By comparing cluster metrics over the four time periods (Table 2), our aim was to understand how ILI, RIDT and S-OIV were able to illustrate the progression and movement of cluster centers, the variability of age-adjusted relative risks, and the size of cluster radii over time. As compared to the full-period (shaded area D: 26 April – 13 May) most clusters could not be identified in the first time period up to April 29th, even though this period encompasses the peak of the outbreak cases (based on ILI), which is estimated to have been around April 28th. However, by the next time period ending 03 May, the County ILI and the Brownsville S-OIV clusters most accurately portrayed the final clusters for the full period in terms of center location, radius, and RR estimate. For the remaining measures at the Brownsville and County extents, the best estimate of the full period were not until all data to 07 May was utilized. For all measures at all extents, the second (B) or third (C) period, the cluster center could be identified within 5 km, the radius within 12% of the full-period, and the RR within ~36%. These findings indicate that the cluster center and radius, as well as the anticipated relative risk to those living within a cluster area may be adequately estimated by real-time outbreak surveillance, perhaps as early as just after the peak incidence.

Of interest to public health officials is the early identification of areas in greatest need of intervention. We found both rates and relative risks of ILI and RIDT to be significantly correlated with full-period S-OIV rates and relative risks at the census block level for all four time periods under study (Table 3). Correlations with S-OIV generally improved as cumulative data was utilized in each successive time period up until the third period (26 April – 07 May) for ILI rates and relative risks at both the County and Brownsville extents. RIDT correlations with S-OIV were strongest utilizing the full period data. Given these findings, ILI may prove to be a better predictor of rates and risks of the outbreak at an earlier time period. This finding is of interest as the collection and analysis of ILI data is often more cost effective and efficient to collect than RIDT results during the course of an outbreak, and both ILI and RIDT do not have the cost and time lag associated with obtaining results of S-OIV from remote (or even local) laboratories.

It is possible that the same individual associated as an S-OIV case was also counted as an RIDT and/or an ILI case in our data set. We know that there is significant overlap between ILI and RIDT reports as all 405 of our RIDT cases were obtained through medical report follow-up on ILI cases. Additionally, while common patterns may have been detectable through the risk, rate and cluster evaluation between the three measures, this study is limited in its ability to distinguish singular cases from those that may have overlapped in measures (ILI and/or RIDT and/or S-OIV). Indeed, one person who visited a clinic with influenza symptoms may be represented in all three measures. However, because the data for this study was examined de-identified with the exception of addresses, duplicates across testing measures could not be distinguished since they could potentially refer to multiple individuals within the same household.

There are also some limitations to be addressed with respect to the population at-risk distribution and the cluster analysis results. In this study, we utilized the data from the most recent complete census: in the year 2000. We assumed that the entire population was at risk in this study due to the fact that the virus was novel and the age-related and other (e.g. pregnant women) risk factors were not known until later. While updated age-stratified population data is available from the U.S. Census Bureau as the American Community Survey, the data is only available at the state and county levels (United States Census

Bureau 2009). The far eastern and northern areas of Brownsville have undergone significant growth since 2000 relative to some other areas, and this may have biased the denominator in our calculations, resulting in a higher relative risk being assigned to the outlying areas than was the case given the actual population in 2009.

Finally, it is well known that the use of a spatial scan statistic may result in potential bias due to what is referred to as the 'edge effect' where areas along the edge of a region being studied can be misclassified because data outside the region are not considered in the analysis. The scanning window may extend into areas outside the study region to include a neighboring area (e.g. census block group) for which there are no data. If the neighboring area has no population at risk, such as an ocean, this edge effect is controlled for because no cases will exist. In this analysis there were no cases of ILI, RIDT, or S-OIV in the areas directly east of the Brownsville extent (Fig. 3 a, c, e) so this effect likely played little role in the final results.

CONCLUSION

The results presented here suggest that ILI and RIDT spatiotemporal analysis may be useful in understanding the nature of S-OIV outbreaks in space and time, ultimately informing real-time intervention and control such that outbreak impacts are minimized.

The threat from S-OIVs has yet to be sufficiently understood, but these viruses have the potential to significantly impact human health and the global economy (Fraser et al. 2009; Itoh et al. 2009). This work may be prospectively testable in a very short time frame. As of the late fall 2009, swine-origin influenza had returned. On 24 October 2009, with an estimated 1,000 deaths in the U.S. since March, President Barack Hussein Obama issued a proclamation declaring the 2009 H1N1 influenza pandemic a national emergency (Obama 2009). Looking forward, if other, more efficient measures are indicative of the nature of an outbreak, the application of this work could be utilized in more efficient assessments of small-area clusters in real-time coupled with community health efforts in standard type-A flu outbreaks or recombinant S-OIV viruses (Neumann et al. 2009). An understanding and appreciation of real-time surveillance methods that effectively and efficiently inform when and where local intervention should be focused will be critical to minimizing the impact of future outbreaks on local communities.

Acknowledgments

This work was supported in part by DMID Contract 09-0032 Vaccine and Treatment Evaluation Unit N02A1025465, MD000170 P20 funded from the National Center on Minority Health and Health disparities (NCMHD), and the University of Texas Houston Health Sciences Center, Center for Clinical and Translational Science CCTS-CTSA award 1U54RR023417-01 funded by the National Center for Research Resources (NCRR).

We acknowledge the contribution and support of many members of the S-OIV outbreak response team. From the Cameron County Department of Health and Human Services we thank Gabriela Saucedo, Edgar Martinez, Juanita Escamilla, Esmeralda Guajardo, Pedro Hinojosa and Sandra De La Cruz. From the University of Texas Health Science Center School of Public Health, Brownsville Regional Campus we thank Lisa Mitchell Bennett, Aulasa Camerlin, Caroline Mullin, Mary Walsh, Rocio Uribe, Elizabeth Braunstein, Julie Ramirez, Blanca Restrepo, Maria Gomez, Christina Villareal, Margarita Ramirez, Adela Rodriguez, Arisve Ramirez, Rosa Saucedo, Magdalena Gutierrez, Angelica Muniz, Marcelina Martinez Villarreal, Mary Beth Lacy, Jennifer Mota, Madan Dang, Mayra Saldana, Alice Gonzalez, Diana Gomez, Lorraine Bautista. From the City of Brownsville, we thank Arturo Rodriguez. From the University of Texas at Brownsville, we thank Anne Rentfro, Consuelo Villalon, Jennifer Brinkworth and Michael Rivas. From the University of Texas at Austin we thank Mitchell McKnight, Katie Hathaway, Kelly Broussard, Meagan Sebring, Sami Miller, Ellen Jones, Priya Davar. For the University of Michigan School of Public Health we thank Laura Dirkes.

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Figure 1.

Cameron County, Texas is situated directly on the US-Mexico border at the mouth on the Rio Grande River and is the nearest point of entry into the United States from the suspected origin of the H1N1 pandemic, La Gloria, in the state of Veracruz, Mexico (a). Brownsville, the largest city in Cameron County, sits directly on the border adjacent to the Mexican city of Matamoros, Tamaulipas (b). Border crossing points and the location of the Cameron County Courthouse are shown (b).

Figure 2
Date distribution curves for 2(a) Influenza-Like Illness (ILI) by date of report, 2(b) Rapid Influenza Diagnostic Tests (RIDT) by date of symptom onset, and 2(c) swine-origin influenza virus (S-OIV) by date of sample. The four time periods of study are indicated: April 26–29 (A); April 30–May 3 (B); May 4–May 7 (C); and May 8–May 14 (D).

May 14(D). RIDT most closely followed the typical epidemiologic curve for a flu outbreak, given that the reporting of data was more consistent and that the measure was date of symptom onset. Even though RIDT symptoms onset were recorded prior to April 26, we started our study on this date due to the fact that ILI and S-OIV data were first available on that date.

Figure 3

Quintiles of raw rates per 100,000 population and geocoded address points of cases for all three influenza measures: influenza-like illness (ILI: a, b); rapid influenza diagnostic tests (RIDT: c, d); and swine-origin influenza virus (S-OIV: e, f) at the Cameron County, Texas (a, c, e) and Brownsville (b, d, f) extents during the spring 2009 novel A H1N1 influenza pandemic. Data shown is for the study period 26 April – 13 May. Full scales and legends for scale and all common features (border crossing, river, Brownsville extent) are provided at the base of Fig. 3 (a, b).

Figure 4
Brownsville-extent space-time age-adjusted relative risks and clusters for influenza-like illness (a); rapid influenza diagnostic tests (b); and swine-origin influenza virus (c); for the full outbreak time period 26 April – 13 May.

Table 1

Space-only and space-time cluster results for time period 26 April – 13 May for influenza-like illness (ILI), rapid influenza diagnostic tests (RIDT), and swine-origin influenza virus (S-OIV).

Measure	Extent	Space/Time ¹	Loc ²	R ³	OBS ⁴	EXP ⁵	RR ⁶	p ⁷	Cluster dates ⁸
ILI	County	Space	51°, 6.78	13.56	977	621.6	3.64	0.001	
ILI	County	Space-Time	51°, 6.78	13.56	673	271.7	4.28	0.001	April 28 – May 5
RIDT	County	Space	51°, 6.78	13.56	207	131.8	3.57	0.001	
RIDT	County	Space-Time	51°, 6.78	13.56	165	53.79	7.39	0.001	April 26 – May 3
S-OIV	County	Space	77°, 6.57	6.6	116	60.79	3.08	0.001	
S-OIV	County	Space-Time	74°, 8.18	7.69	74	23.72	4.45	0.001	April 27 – May 4
ILI	Brownsville	Space	101°, 9.50	0	35	5.14	7.03	0.001	
ILI	Brownsville	Space-Time	99°, 5.17	5.1	371	184.2	2.66	0.001	April 29 – May 5
RIDT	Brownsville	Space	101°, 9.50	7.34	116	80.8	2.04	0.001	
RIDT	Brownsville	Space-Time	101°, 9.50	8.37	96	34.1	4.75	0.001	April 26 – May 2
S-OIV	Brownsville	Space	71°, 10.30	8.81	97	74.2	1.86	0.057	
S-OIV	Brownsville	Space-Time	71°, 10.30	8.81	56	22.94	3.4	0.001	April 27 – May 2

¹ Space-time takes into account the date for cases of each respective measure;

² Cluster center location bearing (°east of north), distance (km) from Cameron County Courthouse reference point;

³ Radius (km) of the cluster. A cluster with a zero radius indicates that the cluster was contained within a single census block-group ;

⁴ Observed cases in cluster;

⁵ Expected cases in cluster;

⁶ Age-adjusted relative risk;

⁷ Significance level;

⁸ Date range for cluster (space-time only).

Table 2

Cluster shifts for cumulative time periods A through C relative to full outbreak period D (shaded).

Extent	Loc ¹	R ²	RR ³	26 April – 29 (period A)				26 April – 03 May (period B)				26 April – 07 May (period C)			
				Ad ⁴	R ² (%Δ) ⁵	RR ³ (%Δ) ⁶	Δd ⁴	R ² (%Δ) ⁵	RR ³ (%Δ) ⁶	Δd ⁴	R ² (%Δ) ⁵	RR ³ (%Δ) ⁶	Δd ⁴	R ² (%Δ) ⁵	RR ³ (%Δ) ⁶
26 April – 13 May (D: full study period)															
ILI County	51°, 6.78	13.56	4.28*	8.1	17.13 (26.3)	9.31* (117.5)	0	13.56 (0)	6.69* (56.3)	2.1	11.96 (-11.8)	3.43* (-19.9)			
RIDT County	51°, 6.78	13.56	7.39*	9.1	6.85 (-49.5)	4.5* (-39.1)	12.6	16.05 (18.4)	3.79* (-48.7)	0	13.56 (0)	4.73* (-36.0)			
S-OIV County	74°, 8.18	7.69	4.45*	4.5	11.94 (55.3)	5.33* (19.8)	1.7	6.6 (-14.2)	5.12* (15.1)	0	7.49 (-2.6)	4.14* (-7.0)			
ILI Brownsville	99°, 5.17	5.10	2.66*	6.2	8.85 (73.5)	3.51* (32.0)	4.1	6.94 (36.1)	3.21* (20.7)	0	5.10 (0)	2.16* (-18.8)			
RIDT Brownsville	101°, 9.50	8.37	4.75*	4.1	6.85 (-18.2)	2.91* (-38.7)	4.1	6.85 (-18.2)	3.16* (-33.5)	5.1	8.81 (5.3)	3.66* (-22.9)			
S-OIV Brownsville	71°, 10.30	8.81	3.4*	2.2	6.94 (-21.2)	3.28* (-3.5)	0	8.81 (0)	2.98* (-12.4)	0	8.81 (0)	2.69* (-20.9)			

* Significance (*p*) to the 0.001 level

¹ Cluster center location bearing (°east of north), distance (km) from Cameron County Courthouse reference point;

² Radius of cluster in km

³ Age-adjusted relative risk (RR) of the cluster

⁴ Distance (km) of cluster center as compared to full study period (26 April – 13 May) cluster center

⁵ Percent change in radius of cluster as compared to full study period (26 April – 13 May) cluster radius

⁶ Percent change in relative risk as compared to RR of full study period (26 April – 13 May) cluster relative risk

Table 3

Correlation between ILI/RIDT Rates and Relative Risk for various time intervals and S-OIV for the entire study period.

Rate		Extent	26 April – 29	26 April – 03 May	26 April – 07 May	26 April – 13 May (full period)
ILI	County		0.435**	0.580**	0.670**	0.649**
	Brownsville		0.358**	0.511**	0.646**	0.633**
RIDT	County		0.368**	0.526**	0.592**	0.593**
	Brownsville		0.334**	0.488**	0.566**	0.577**
Relative Risk						
ILI	County		0.404**	0.504**	0.638**	0.618**
	Brownsville		0.330**	0.427**	0.625**	0.608**
RIDT	County		0.319**	0.458**	0.542**	0.543**
	Brownsville		0.277**	0.412**	0.516**	0.524**

** Correlation is significant at the 0.01 level (2-tailed).