Multistate analysis of prospective Legionnaires’ disease cluster detection using SaTScan, 2011–2015

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Abstract

Detection of clusters of Legionnaires’ disease, a leading waterborne cause of pneumonia, is challenging. Clusters vary in size and scope, are associated with a diverse range of aerosol-producing devices, including exposures such as whirlpool spas and hotel water systems typically associated with travel, and can occur without an easily identified exposure source. Recently, jurisdictions have begun to use SaTScan spatio-temporal analysis software prospectively as part of routine cluster surveillance. We used data collected by the Active Bacterial Core surveillance platform to assess the ability of SaTScan to detect Legionnaires’ disease clusters. We found that SaTScan analysis using traditional surveillance data and geocoded residential addresses was unable to detect many common Legionnaires’ disease cluster types, such as those associated with travel or a prolonged time between cases. Additionally, signals from an analysis designed to simulate a real-time search for clusters did not align with clusters identified by traditional surveillance methods or a retrospective SaTScan analysis. A geospatial analysis platform better tailored to the unique characteristics of Legionnaires’ disease epidemiology would improve cluster detection and decrease time to public health action.

Introduction

Legionnaires’ disease, a severe pneumonia typically caused by inhalation of aerosolized water containing Legionella bacteria, is responsible for more than 7,400 reported illnesses annually...
in the United States (U.S.) [1, 2] though this likely underestimates the true burden of disease [3]. Clusters, which more than tripled from 2009–2017 [4], can be large, resulting in significant morbidity and mortality [5–8], or small [9, 10], which makes rapid detection challenging. Additionally, environmental sources implicated in clusters include cooling towers, which can transmit bacteria for miles [11], showers or other potable water sources, whirlpool spas, and decorative water features such as fountains [12]. Identification of an exposure source often requires reviewing potential environmental exposures during the ‘incubation period’ (defined as the 10–14 days before disease onset) and comparing bacterial isolates collected from environmental and clinical samples. Clinical isolates have become increasingly rare since the widespread uptake of urinary antigen testing. A lack of clinical isolates, failure to identify epidemiologic links among cases, and a large number of possible environmental sources can complicate cluster detection. Thus, the true burden of sporadic (cases with no known epidemiologic or molecular links) versus cluster-associated Legionnaires’ disease is not fully understood.

Legionnaires’ disease clusters can have widely varying characteristics. Those associated with travel typically have a readily identifiable common exposure (such as a single hotel), simplifying their detection. Most travel clusters involve two or three cases, which is enough to trigger a public health investigation [13]. In contrast, community clusters often do not begin with a known shared exposure, making them more difficult to detect and investigate. In the absence of factors that could simplify identification such as a sharp spike in cases, unusual geographic clustering, or a very low baseline of disease, these clusters can remain undetected. Spatio-temporal analysis software has been previously used for multiple conditions to detect cases of disease that may have an unidentified spatial or temporal association [14–24]. One method that has gained traction as part of public health surveillance activities is the SaTScan prospective space-time permutation scan statistic [25, 26]. This analysis technique was designed to identify increases in disease across both space and time above the historic baseline to speed detection of potential clusters. While originally developed for use with syndromic data, recently it has been utilized to detect primarily community-associated clusters of Legionnaires’ disease in real time [27–29]. While promising, this method may not be ideal for detection of smaller clusters [30] or those occurring over a prolonged time [20] that may also be missed by astute clinicians or public health professionals.

We analyzed geocoded Legionnaires’ disease case data collected by the Active Bacterial Core surveillance platform, using SaTScan to simulate real-time detection of clusters across multiple states. We then compared these results to a retrospective SaTScan analysis and historic records of Legionnaires’ disease investigations to assess the strengths and limitations of the prospective space-time permutation scan statistic as an adjunct to traditional Legionnaires’ disease cluster detection methods.

**Materials and methods**

Data collection and analysis activities conducted as part of the Active Bacterial Core surveillance system have been reviewed at CDC and designated as non-research.

**Active Bacterial Core surveillance (ABCs) system**

Legionnaires’ disease surveillance through the ABCs platform has been previously described [31]. Briefly, laboratory-confirmed Legionnaires’ disease cases among residents of 10 surveillance areas (5 complete states and 5 defined catchments within states) representing all U.S. census regions were identified from 2011–2015. A confirmed case was defined as the isolation of *Legionella* from respiratory culture, detection of *Legionella* antigen in urine, or
seroconversion (a more than fourfold rise in antibody titer between acute and convalescent sera) to *Legionella pneumophilla* serogroup 1, in addition to clinically compatible symptoms [31]. Information on patient demographics, illness symptoms, underlying conditions, disease onset date, and laboratory testing information were abstracted from medical records. Residence information was geocoded to the census tract level by participating jurisdictions and securely transmitted to CDC for analysis.

**Census data**

Data from the 2010 decennial census were acquired from the U.S. Census Bureau to calculate demographic and geographic characteristics of census tracts within the ABCs Legionnaires’ disease catchment areas.

To generate the required coordinates file, TIGER/Line shape files were obtained from the U.S. Census Bureau (https://www.census.gov/geo/maps-data/data/tiger-line.html) for each of the ten ABCs states. The latitude and longitude of each census tract’s centroid were extracted. All census tracts that fell outside of the ABCs Legionnaires’ disease catchment areas were removed.

**Historical Legionnaires’ disease cluster information**

Data on traditionally identified Legionnaires’ disease clusters from 2012–2015 within ABCs jurisdictions was requested from participating health departments. Clusters were defined as any grouping of cases requiring a public health investigation. Factors resulting in a full investigation likely varied by jurisdiction. Data included onset dates for the first and last confirmed case, the county where the cluster occurred, and the type of cluster (e.g., travel, healthcare, community).

**SaTScan analysis**

We used SaTScan 9.4.4 in both prospective and retrospective analysis modes.  

**Prospective analysis.** To simulate methods currently utilized by some health departments [20, 27], we used SAS Enterprise Guide 7.1.1 (Cary, NC) and the SaTScan prospective space-time permutation scan statistic to search for clusters. SAS EG was used to generate the SaTScan parameter files for each analysis run. Each analysis was run at the state level using a maximum temporal cluster size of 90 days (time between first and last case onset dates). This timeframe was chosen to decrease the baseline data required for analysis and to investigate methods currently in use by health departments. The time aggregation was 1 day, the minimum cluster length was 2 days, and an adjustment for day-of-the-week by space interaction was performed. We also chose to ignore clusters centered in other clusters to decrease the number of duplicate signals identified in a given timeframe. Finally, the maximum spatial cluster size was set to 6 kilometers. This was chosen based on the reported size for large community-style clusters. All other analytic options were left at their default values. Each run utilized 1 year of data. For the first run, the start and end dates were January 1, 2011, and January 1, 2012. These dates were then incremented by one day and the analysis was repeated until all 2012 data were included. The analysis was then restarted for 2013 and similarly looped until all subsequent days and years through 2015 had been included. In total, 1,460 individual analyses were performed. Case onset date was used when available; otherwise, the collection date for the confirmatory laboratory specimen was used. Signals were detected at two statistical thresholds (p<0.05 or p<0.01). These thresholds were chosen based on current SaTScan cluster detection efforts in use by New York State (unpublished) and New York City [27], respectively. Detected signals
were compared to information from traditionally identified Legionnaires’ disease cluster investigations.

**Retrospective analysis.** To detect clusters retrospectively, SaTScan was run in batch mode from the command line at the state level using all 5-years of available surveillance data, 2011–2015. Other than the use of retrospective space-time analysis mode, no other settings were changed from the prospective analysis.

**Results**

**ABCs Legionnaires’ disease case and outbreak surveillance data**

From 2011–2015, 2527 confirmed cases of Legionnaires’ disease were identified by the ABCs network (Table 1). Census tract information was available for 2329 (92%) cases. Cases clustered geographically; 32% of census tracts contained a confirmed case.

Catchment areas varied in population density (957 persons/mi$^2$ in New Mexico to 9190 persons/mi$^2$ in California) and building density (410–3393 median houses/mi$^2$ in the same two states). Most (87%) included counties were classified as urban according to the 2010 decennial census.

Of the 36 traditionally identified Legionnaires’ disease clusters reported by health departments (Table 2), 39% were classified as travel-associated (related to a single public accommodation), followed by community/residential (36%), and healthcare-associated (25%).

**Table 1. Descriptive information on confirmed LD cases by ABCs catchment area (2011–2015).**

| State | Statewide catchment area? | Total confirmed cases | Median cases per year (range) | Total census tracts in catchment area | Median pop per sq. mi. (range) | Median houses per sq. mi. (range) | % pop urban Census tracts with any cases |
|-------|---------------------------|-----------------------|------------------------------|--------------------------------------|-------------------------------|-----------------------------------|---------------------------------------|
| CA    | N                         | 80                    | 12 (11–29)                   | 766                                  | 9190 (4232–17905)             | 3393 (1659–7122)               | 99.6% 67                               |
| CO    | N                         | 174                   | 30 (15–54)                   | 587                                  | 4397 (2540–6527)              | 1856 (986–2627)                | 96.3% 131                              |
| CT    | Y                         | 316                   | 58 (57–79)                   | 833                                  | 1961 (715–4940)               | 817 (266–2042)                 | 88.0% 233                              |
| GA    | N                         | 151                   | 30 (20–47)                   | 699                                  | 2570 (1735–3755)             | 1062 (673–1671)                | 97.7% 131                              |
| MD    | Y                         | 714                   | 144 (115–158)                | 1406                                 | 3219 (824–6493)              | 1277 (336–2695)                | 87.2% 493                              |
| MN    | Y                         | 236                   | 51 (28–55)                   | 1338                                 | 1463 (71–3689)               | 601 (32–1598)                  | 73.3% 203                              |
| NM    | Y                         | 56                    | 10 (9–16)                    | 499                                  | 957 (50–3767)                | 410 (22–1465)                 | 77.4% 39                                |
| NY    | N                         | 410                   | 86 (62–104)                  | 557                                  | 1656 (196–4530)              | 653 (78–2050)                 | 74.3% 259                              |
| OR    | Y                         | 142                   | 22 (19–49)                   | 834                                  | 2204 (144–5000)              | 922 (64–2073)                  | 81.0% 127                              |
| TN    | N                         | 248                   | 42 (24–103)                  | 888                                  | 1511 (421–2908)              | 651 (172–1316)                | 82.5% 109                              |

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**Table 2. Descriptive information from traditionally identified clusters by reporting state.**

| State | Number of clusters | Median cases (range) | Median length (days, range) | Travel clusters | Healthcare clusters | Community/Residential |
|-------|--------------------|----------------------|-----------------------------|-----------------|---------------------|-----------------------|
| CA    | 1                  | 2                    | 3                           | 1               | 0                   | 0                     |
| CO    | 4                  | 3 (2–9)              | 21 (2–90)                   | 3               | 0                   | 1                     |
| CT    | 2                  | 7 (6–7)              | 33 (22–43)                  | 0               | 0                   | 2                     |
| GA    | 3                  | 2 (2–10)             | 95 (10–180)                 | 1               | 0                   | 2                     |
| MD    | 11                 | 2 (2–7)              | 43 (4–306)                  | 5               | 1                   | 5                     |
| MN    | 3                  | 2                    | 15 (2–24)                   | 1               | 1                   | 1                     |
| NM    | 0                  | -                    | -                           | -               | -                   | -                     |
| NY    | 7                  | 2 (2–6)              | 83 (63–381)                 | 0               | 7                   | 0                     |
| OR    | 1                  | 4                    | 1101                        | 1               | 0                   | 0                     |
| TN    | 4                  | 3 (2–3)              | 31 (30–184)                 | 2               | 0                   | 2                     |

1Data not available for entire ABCs catchment area.
2First and last onset date estimated.

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cluster size was 2 cases (2–10). Clusters varied in length, from 2–1101 days between the first and last case onset dates.

Some outbreak investigations (19/36, 53%) had factors that made them incompatible with detection using our prospective SaTScan analysis methodology. Most of these clusters involved travel away from the home (14/19, 74%). These could not be detected due to a lack of geocoded exposure data both from patients residing in the search area and those traveling from other jurisdictions. Other clusters in this category include those with a prolonged time between cases (5/19, 26%). These were not detectable due to the maximum temporal window chosen for this study.

### Prospective SaTScan analysis

The simulated prospective analysis identified 39 unique signals (p<0.05) (Table 3). A unique signal was defined as one that did not substantially overlap in space and time with other

| State | Signals | Median recurrence interval (range) | Median cases (range) | Median Cluster radius (km,range) | # of health department clusters detected |
|-------|---------|-----------------------------------|----------------------|---------------------------------|----------------------------------------|
| CA    | p<0.05  | 0                                 | -                    | -                               | 0                                      |
|       | p<0.01  | 0                                 | -                    | -                               | 0                                      |
| CO    | p<0.05  | 3                                 | 100 (21–100)         | 4 (3–5)                         | 5.76 (4.99–5.77)                       | 0                                      |
|       | p<0.01  | 0                                 | -                    | -                               | -                                      | 0                                      |
| CT    | p<0.05  | 4                                 | 40 (32–53)           | 3 (2–5)                         | 4.69 (0–5.51)                         | 0                                      |
|       | p<0.01  | 0                                 | -                    | -                               | -                                      | 0                                      |
| GA    | p<0.05  | 2                                 | 53 (29–77)           | 3                               | 5.56 (5.87–5.24)                      | 0                                      |
|       | p<0.01  | 0                                 | -                    | -                               | -                                      | 0                                      |
| MD    | p<0.05  | 15                                | 81 (22–880)          | 4 (3–6)                         | 4.28 (1.03–5.86)                      | 0                                      |
|       | p<0.01  | 6                                 | 145 (104–880)        | 5 (3–6)                         | 4.05 (3.09–5.78)                      | 0                                      |
| MN    | p<0.05  | 4                                 | 28 (23–91)           | 3 (2–3)                         | 5.13 (1.66–5.76)                      | 0                                      |
|       | p<0.01  | 0                                 | -                    | -                               | -                                      | 0                                      |
| NM    | p<0.05  | 0                                 | -                    | -                               | -                                      | 0                                      |
|       | p<0.01  | 0                                 | -                    | -                               | -                                      | 0                                      |
| NY    | p<0.05  | 4                                 | 44 (28–100)          | 6 (3–14)                        | 4.86 (1.54–5.99)                      | 0                                      |
|       | p<0.01  | 0                                 | -                    | -                               | -                                      | 0                                      |
| OR    | p<0.05  | 2                                 | 101 (21–180)         | 3 (2–3)                         | 4.78 (4.30–5.26)                      | 0                                      |
|       | p<0.01  | 1                                 | 180                  | 3                               | 4.30                                  | 0                                      |
| TN    | p<0.05  | 5                                 | 37 (26–91)           | 3 (2–4)                         | 3.93 (3.53–5.13)                      | 0                                      |
|       | p<0.01  | 0                                 | -                    | -                               | -                                      | 0                                      |

Reccurrence interval varies inversely with the p-value and represents the number of surveillance days required to detect a similarly significant signal by chance

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signals. None of the prospectively detected signals matched a traditionally identified cluster. Of the detected signals, seven met the more stringent significance threshold ($p < 0.01$).

**Retrospective SaTScan analysis**

No significant signals ($p < 0.05$) were identified by retrospective analysis.

**Discussion**

Our analysis indicates that, when standard spatial and temporal settings are utilized in a range of localities across 10 states, the SaTScan prospective space-time permutation scan statistic is not well suited for real-time detection of common types of Legionnaires’ disease clusters. This includes those associated with travel, those with a small number of cases, or those with a prolonged time between cases. Additionally, we found that signals detected by prospective SaTScan using multiple statistical thresholds ($p < 0.05$ or $p < 0.01$) were not identified by retrospective SaTScan or traditional methods. This discordance indicates that signals detected prospectively may not represent a true increase in cases.

During our study period, more than half of reported Legionnaires’ disease clusters health departments investigated would not have been detected using surveillance data and program settings commonly used as part of routine prospective SaTScan analyses. This was due to travel-association and a prolonged cluster length of $>90$ days, which are characteristics common among recognized Legionnaires’ disease clusters. Without geocoded exposure information collected from patients residing both in state and in other public health jurisdictions, space-time detection of travel clusters is unlikely. Additionally, a Legionnaires’ disease cluster detection strategy should be sensitive enough to detect as few as two cases associated with a single public accommodation (such as a hotel or healthcare facility) over a 12-month period, as that scenario should prompt a full public health investigation. These types of clusters are often associated with potable water systems, involve few cases, and may last for months or even years. Because of these factors, the addition of prospective SaTScan analysis is unlikely to improve detection of the most common types of Legionnaires’ disease clusters identified by public health authorities during our study period.

Our prospective SaTScan analysis also failed to detect traditionally identified clusters that did not involve travel or a prolonged length. This may have been due to the low number of cases associated with many of the reported clusters. This is common in Legionnaires’ disease clusters because of the low attack rate. Previous analyses have shown that SaTScan does not perform well at detecting small clusters [30], which is also the type of cluster most likely to go unrecognized by routine public health surveillance. An explosive increase in cases, such as the 2015 Bronx cluster in New York City [5], may be detected by SaTScan sooner than more traditional surveillance methods but is unlikely to go unrecognized. While timely detection of clusters is important, this benefit may decrease in areas with a lower background rate of disease, as a sharp increase in cases may be more pronounced and thus easier to detect using traditional surveillance methods.

We also found that using prospective SaTScan for cluster detection produced signals that were not found in the retrospective analysis. This strengthens our belief that these signals do not represent a true increase in disease. The ability of retrospective SaTScan analysis to detect unusual spatiotemporal associations has been shown for many other infectious diseases and non-infectious conditions such as cancer [32]. The retrospective method utilizes all available surveillance data and can identify an unusual increase in cases from any point in the study period. Conversely, prospective analysis is limited to the identification of clusters that are currently occurring. While retrospective detection of clusters is not useful for real-time
surveillance purposes, neither is the detection of signals which, when analyzed in a larger histori- cal context, are no longer statistically significant. While the reasons for the lack of concor- dance were not determined, we observed that no prospective SaTScan signals were identified by the retrospective method or were confirmed by traditional identification methods. Reduc- ing the statistical threshold for the prospective analysis to \( p < 0.01 \) did decrease the number of detected signals, though the lack of overlap with other detection methods remained.

The ideal scenario for SaTScan detection of Legionnaires’ disease clusters is likely a dense urban area with a high background rate of disease and a large number of aerosolizing devices such as cooling towers. Under these conditions, public health officials may struggle to deter- mine if multiple geographically and temporally clustered cases without a known exposure source are related and thus warrant investigation. This may explain the success of SaTScan as part of routine cluster detection in locations such as New York City [33]. Other areas with a lower population density and fewer cases may rarely see the type of rapid increase in cases that SaTScan is most effective at detecting. Additionally, the lack of geocoded exposure location data from within or across jurisdictions is a significant hurdle to detection of many common cluster types. Collecting this information would be beneficial for any jurisdiction considering the adoption of geospatial cluster detection as part of routine surveillance activities.

This study had a number of limitations. First, limited descriptive information was available for clusters reported by participating states, including whether a clear exposure source was identified. Second, we only received geolocation data for patient residence. While this is a data element commonly collected by routine public health surveillance, previous studies have shown that additional location data (such as work address) can improve cluster detection [28]. Similarly, collection of possible exposure location data could aid in detection of clusters involving travel to a nearby location such as a healthcare facility. We also were unable to investigate signals produced by the prospective analysis to determine if they represent unidentified clusters. This prevents us from saying with certainty that these signals represent false positives. Finally, we did not control for possible changes in the spatial distribution of the population within each catchment area over the study period.

SaTScan software can use routinely collected surveillance data, requires minimal computer programming expertise, and is not time- or resource-intensive to operate. However, we found that the prospective space-time scan statistic utilized by SaTScan is unable to detect many Legionnaires’ disease cluster types using commonly collected geolocation data and analysis set- tings. Signals produced by the prospective analysis were not confirmed by other detection methods. Additional research is needed to fully understand the reasons for the lack of concor- dance between different SaTScan analysis methods. If this type of analysis is used for real-time cluster detection, reasonable action thresholds may help ensure that findings require a public health investigation. Spatial detection methods more tailored to the epidemiologic and environ- mental characteristics of Legionnaires’ disease are needed to improve cluster detection and accelerate public health action.

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Disclaimers: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the authors’ affiliated institutions. Use of trade names, commercial sources or private organiza- tions is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services and/or CDC.

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**References**

1. Fields BS, Benson RF, Besser RE. Legionella and Legionnaires' disease: 25 years of investigation. Clin Microbiol Rev. 2002; 15(3):506–26. https://doi.org/10.1128/CMR.15.3.506-526.2002 PMID: 12097254; PubMed Central PMCID: PMCPMC118082.

2. Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System, Weekly Tables of Infectious Disease Data. Atlanta, GA. CDC Division of Health Informatics and Surveillance. Available at: https://www.cdc.gov/nndss/infectious-tables.html.

3. Marston BJ, Plouffe JF, File TM Jr., Hackman BA, Salstrom SJ, Lipman HB, et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance Study in Ohio. The Community-Based Pneumonia Incidence Study Group. Arch Intern Med. 1997; 157(15):1709–18. Epub 1997/08/11. https://doi.org/10.1001/archinte.1997.00440360129015 PMID: 9250232.

4. Centers for Disease Control and Prevention. National Outbreak Reporting System, NORS Dashboard. Atlanta, GA. CDC National Center for Emerging and Zoonotic Infectious Diseases. Available at: https://wwwn.cdc.gov/norsdashboard/.

5. Weiss D, Boyd C, Rakeman JL, Greene SK, Fitzhenry R, McProud T, et al. A Large Community Outbreak of Legionnaires’ Disease Associated With a Cooling Tower in New York City, 2015, Public Health Rep. 2017; 132(2):241–50. https://doi.org/10.1177/0033354916689620 PMID: 28141970; PubMed Central PMCID: PMCPMC5349480.

6. Demirjian A, Lucas CE, Garrison LE, Kozak-Muiznik NA, States S, Brown EW, et al. The importance of clinical surveillance in detecting legionnaires’ disease outbreaks: a large outbreak in a hospital with a
Legionella disinfection system—Pennsylvania, 2011–2012. Clin Infect Dis. 2015; 60(11):1596–602. https://doi.org/10.1093/cid/civ153 PMID: 25722201.

7. Smith SS, Ritger K, Samala U, Black SR, Okodua M, Miller L, et al. Legionellosis outbreak associated with a hotel fountain. Open forum infectious diseases. 2015; 2(4):ofv164. Epub 2015/12/31. https://doi.org/10.1093/ofid/ofv164 PMID: 25722201. PubMed Central PMCID: PMCPM6492259.

8. Greig JE, Carnie JA, Tallis GF, Ryan NJ, Tan AG, Gordon IR, et al. An outbreak of Legionnaires’ disease at the Melbourne Aquarium, April 2000: investigation and case-control studies. The Medical journal of Australia. 2004; 180(11):566–72. Epub 2004/06/04. PMID: 15174987.

9. McEvoy M, Batchelor N, Hamilton G, MacDonal A, Fairers M, Sills A, et al. A cluster of cases of legionnaires’ disease associated with exposure to a spa pool on display. Communicable disease and public health. 2000; 3(1):43–5. Epub 2000/04/01. PMID: 10743318.

10. Palmore TN, Stock F, White M, Bordner M, Michelin A, Bennett JE, et al. A cluster of cases of nosocomial legionnaires disease linked to a contaminated hospital decorative water fountain. Infection control and hospital epidemiology. 2009; 30(8):764–8. Epub 2009/07/08. https://doi.org/10.1086/598855 PMID: 19580436; PubMed Central PMCID: PMCPM2868954.

11. Addiss DG, Davis JP, Laventure M, Wand PJ, Hutchinson MA, McKinney RM. Community-Acquired Legionnaires’ Disease Associated with a Cooling Tower: Evidence for Longer-Distance Transport of Legionella Pneumophila. American Journal of Epidemiology. 1989; 130(3):557–68. https://doi.org/10.1093/aje/a115370 PMID: 2764000.

12. CDC. Surveillance for travel-associated legionnaires disease—United States, 2005–2006. Morb Mortal Wkly Rep. 2007; 56(48):1261–3.

13. Glatman-Freedman A, Kaufman Z, Kopel E, Bassal R, Taran D, Valinsky L, et al. Using the Kulldorff’s scan statistical analysis to detect spatio-temporal clusters of tuberculosis in Qinghai Province, China, 2009–2016. BMC infectious diseases. 2017; 17(1):578. Epub 2017/08/23. https://doi.org/10.1186/s12879-017-2643-y PMID: 28826399; PubMed Central PMCID: PMCPMC5556389.

14. Bull M, Hall IM, Leach S, Robesyn E. The application of geographic information systems and spatial data during Legionnaires’ disease outbreak responses. Eurosurveillance. 2012; 17(49). https://doi.org/10.2807/esu.17.49.20331-en

15. Bull M, Hall IM, Leach S, Robesyn E. The application of geographic information systems and spatial data during Legionnaires’ disease outbreak responses. Eurosurveillance. 2012; 17(49). https://doi.org/10.2807/esu.17.49.20331-en

16. Okris LT, Peterson ER, Brooks MM, Mertz KJ, Harrison LH, Stout JE, et al. Simulation of Legionnaires’ disease prospective spatiotemporal cluster detection, Allegheny County, Pennsylvania, USA. Epidemiology and Infection. 2018; 1–9. Epub 2018/10/18. https://doi.org/10.1017/s0950268818002789 PMID: 30334502

17. Greene SK, Kulldorff M, Huang J, Brand RJ, Kleinman KP, Hsu J, et al. Timely detection of localized excess influenza activity in Northern California across patient care, prescription, and laboratory data. Stat Med. 2011; 30(5):549–59. Epub 2011/02/12. https://doi.org/10.1002/sim.3883 PMID: 21312219; PubMed Central PMCID: PMCPMC3058686.

18. Greene SK, Huang J, Abrams AM, Gilliss D, Reed M, Platt R, et al. Gastrointestinal disease outbreak detection using multiple data streams from electronic medical records. Foodborne Pathog Dis. 2012; 9 (5):431–41. Epub 2012/03/21. https://doi.org/10.1089/fpd.2011.1036 PMID: 22429155; PubMed Central PMCID: PMCPMC3377951.
23. Yih WK, Deshpande S, Fuller C, Heisey-Grove D, Hsu J, Kruskal BA, et al. Evaluating real-time syndromic surveillance signals from ambulatory care data in four states. Public Health Rep. 2010; 125(1):111–20. Epub 2010/04/21. https://doi.org/10.1177/003335491012500115 PMID: 20402203; PubMed Central PMCID: PMCPMC2789823.

24. Sansom P, Copley VR, Naik FC, Leach S, Hall IM. A case-association cluster detection and visualisation tool with an application to Legionnaires’ disease. Stat Med. 2013; 32(20):3522–38. https://doi.org/10.1002/sim.5765 PMID: 23483594; PubMed Central PMCID: PMCPMC3842591.

25. Kulldorff M, Heffernan R, Hartman J, Assuncao R, Mostashari F. A space-time permutation scan statistic for disease outbreak detection. PLoS Med. 2005; 2(3):e59. https://doi.org/10.1371/journal.pmed.0020059 PMID: 15719066; PubMed Central PMCID: PMCPMC548793.

26. Kulldorff M. SaTScan v9.4.4: software for the spatial and space-time scan statistics: Information Management Services, Inc; [cited 2018]. Available from: http://www.satscan.org.

27. Greene SK, Peterson ER, Kapell D, Fine AD, Kulldorff M. Daily Reportable Disease Spatiotemporal Cluster Detection, New York City, New York, USA, 2014–2015. Emerg Infect Dis. 2016; 22(10):1808–12. https://doi.org/10.3201/eid2210.160097 PMID: 27648777; PubMed Central PMCID: PMCPMC5038417.

28. Peterson ER, Greene SK. Spatio-Temporal Cluster Detection for Legionellosis using Multiple Patient Addresses. Online Journal of Public Health Informatics. 2017; 9(1):e121. https://doi.org/10.5210/ojphi.v9i1.7705 PMC5476232.

29. Levin-Rector A, Wilson EL, Fine AD, Greene SK. Refining historical limits method to improve disease cluster detection, New York City, New York, USA. Emerg Infect Dis. 2018; 21(2):265–72. https://doi.org/10.3201/eid2102.140098 PMID: 25625936; PubMed Central PMCID: PMCPMC4313630.

30. Mathes RW, Lail R, Levin-Rector A, Sell J, Paladini M, Konty KJ, et al. Evaluating and implementing temporal, spatial, and spatio-temporal methods for outbreak detection in a local syndromic surveillance system. PLoS One. 2017; 12(9):e0184419. https://doi.org/10.1371/journal.pone.0184419 PMID: 28886112; PubMed Central PMCID: PMCPMC5590919.

31. Dooling KL, Toews KA, Hicks LA, Garrison LE, Bachaus B, Zansky S, et al. Active Bacterial Core Surveillance for Legionellosis—United States, 2011–2013. MMWR Morb Mortal Wkly Rep. 2015; 64(42):1190–3. https://doi.org/10.15585/mmwr.mm6442a2 PMID: 26513329.

32. Agost L. Analysis of spatial-temporal clusters of childhood cancer incidence in the province of Cordoba, Argentina (2004–2013). Arch Argent Pediatr. 2016; 114(6):534–43. Epub 2016/11/22. https://doi.org/10.5546/aap.2016.eng.534 PMID: 27869411.

33. Fitzhenry R, Weiss D, Cimini D, Balter S, Boyd C, Alleyne L, et al. Legionnaires’ Disease Outbreaks and Cooling Towers, New York City, New York, USA. Emerg Infect Dis. 2017; 23(11):1769–76. Epub 2017/10/20. https://doi.org/10.3201/eid2311.161584 PMID: 29049017; PubMed Central PMCID: PMCPMC5652439.