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Systematic review

Spatial methods for infectious disease outbreak investigations: systematic literature review

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Investigations of infectious disease outbreaks are conventionally framed in terms of person, time and place. Although geographic information systems have increased the range of tools available, spatial analyses are used relatively infrequently. We conducted a systematic review of published reports of outbreak investigations worldwide to estimate the prevalence of spatial methods, describe the techniques applied and explore their utility. We identified 80 reports using spatial methods published between 1979 and 2013, ca 0.4% of the total number of published outbreaks. Environmental or waterborne infections were the most commonly investigated, and most reports were from the United Kingdom. A range of techniques were used, including simple dot maps, cluster analyses and modelling approaches. Spatial tools were usefully applied throughout investigations, from initial confirmation of the outbreak to describing and analysing cases and communicating findings. They provided valuable insights that led to public health actions, but there is scope for much wider implementation and development of new methods.

Introduction

Detecting and responding to outbreaks of infectious diseases is a key role of front-line public health organisations [1]. The primary reason for conducting an investigation into an outbreak is prevention of further cases through control measures, while other motivations include addressing public or political concerns, evaluating health programmes and advancing understanding of the disease [2]. Investigations are usually cross-agency exercises and conventionally involve examination of the outbreak in terms of person, time and place.

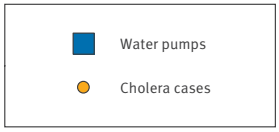
John Snow famously demonstrated the power of plotting the spatial locations of individuals affected in an outbreak [3]. His map of cholera cases in London in 1854 showed a clear pattern that implicated a water pump as the likely source of the illness. Today, guidelines for investigating outbreaks, including the European Centre for Disease Prevention and Control (ECDC) Outbreak Investigation Toolbox, invariably also recommend consideration of case locations [4-7]. Nevertheless, epidemiological investigations of outbreaks, and research into novel approaches for such investigations, have tended to focus more on analysis of person and time than of place [8]. Development of advanced molecular tools, for example, has allowed transmission of infectious agents among populations to be traced with ever increasing detail. Without also considering the spatial aspects of an outbreak, however, important relationships and therefore aetiological insights may be missed [8].

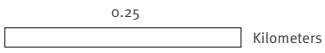
Geographic information systems (GIS) have increased the availability and range of tools that can be used to analyse outbreaks. A GIS is a database designed to handle geographically-referenced information complemented by software tools for the input, management, analysis and display of data [9]. GIS are used widely in epidemiology and the simplest application in an outbreak investigation is to create maps displaying the relative locations of cases, potential sources and/or risk factors. Maps are an engaging and easy-to-understand means of presenting data and can be used to describe patterns, identify outliers and communicate findings. Cases can be plotted using their point locations or aggregated into administrative areas and displayed as rates. Smoothed incidence maps are an alternative means of visualising point locations as continuous distributions of disease risk, generated by adjusting the density at each point according to the number of cases in adjacent areas [9]. Areas can also be demarcated according to locations of potential sources of infection.

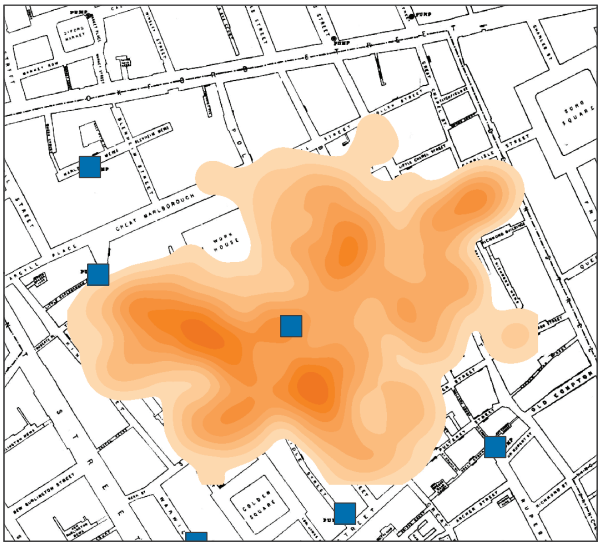
Figure 1

Maps of John Snow's cholera outbreak investigation in London in 1854

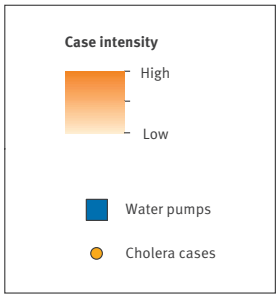
A: Dot map of case locations



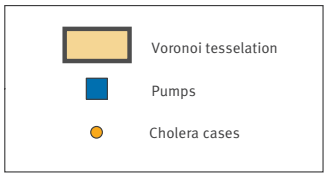




B: Smoothed intensity of case locations



C: Voronoi diagram demarcating area according to nearest water pump



Examples of these different approaches to mapping, using Snow's cholera data, are shown in Figure 1.

Spatial relationships not immediately apparent from maps can also be explored using GIS. Measuring distances from cases to potential sources, for example, can be informative if an infection is suspected to derive from an environmental point source. In outbreaks of Legionnaires' disease, this method has been applied to identify cooling towers or other aerosol-producing devices proximal to the cases and therefore generate hypotheses about the likely source [10]. Integration of additional data in the GIS, such as wind direction, can further aid hypothesis generation, for example by identifying areas most likely to be exposed to air emitted from a suspected source during an outbreak of Q fever [11].

Identification and analysis of clusters, areas with higher than expected levels of disease risk, can trigger and be informative during outbreak investigations. Numerous geostatistical methods have been developed to detect clusters, including methods for point and aggregated data [9,12]. 'Global' tests evaluate the entire area for any evidence of clustering, without pinpointing specific clusters, while 'local' (or 'cluster detection') tests identify the positions of specific clusters. Cuzick and Edwards' *k*-nearest neighbour test, for example, is a global method for assessing clustering in case–control point data [13]. It counts the number of nearest neighbours of cases that are also cases, and compares it to the number that would be expected under the null hypothesis that cases and controls were randomly distributed. Kulldorff's spatial scan statistic is a method used to identify local clustering, usually in point data [14]. Observed numbers of cases within windows of various sizes are compared with numbers that would be expected under a random distribution. Circular or elliptical regions of elevated risk of disease are then located. Scan statistics and the *k*-nearest neighbour test have also been adapted to identify spatiotemporal clustering, testing the null hypothesis that cases geographically close to each other occur at random times [15,16].

Spatial relationships in outbreak data can also be analysed through modelling. A range of techniques can be used which, broadly, aim to create informative representations of features, events and processes in geographical space. Environmental risk mapping, for example, uses statistical methods to define relationships between spatially referenced variables and disease risk [9]. Air dispersion models, meanwhile, can be used to identify spatial locations likely to have been exposed to air-borne infections and infer potential release sites [10].

In this study, we explore through a systematic literature review how methods of spatial visualisation and analysis have been employed in infectious disease outbreak investigations. We aimed to use published reports of outbreak investigations (i) to describe the prevalence, utility and outcomes of applying spatial methods and (ii) to make recommendations for improving practice and identify opportunities for further development in this area.

Methods

Search strategy and selection criteria

The aim of our literature search was to identify published reports of infectious disease outbreak investigations that used spatial methods. We defined an outbreak as the occurrence of a series of cases of disease in excess of the number expected in a given time and place. We focused only on outbreaks with local or regional impact and excluded large national or multinational studies of epidemics or pandemics, such as pandemic influenza. Studies describing retrospective analyses of outbreaks that used spatial methods which could theoretically be applied in real-time investigations were included.

We employed a broad search strategy of multiple electronic databases with few restrictions in order to minimise the risk of bias: We searched Embase, Medline and Web of Science for items with terms relating to spatial analysis ('spatial', 'cluster', 'geographic information systems', 'GIS', 'mapping') and outbreaks ('disease outbreak', 'outbreak', 'epidemic'). The search was run on 28 November 2013 and restricted to articles published after 1980 (Embase), 1946 (Medline) and 1900 (Web of Science). No exclusions were made on basis of language or location, and articles were not limited to human disease. Additional relevant articles known to the authors that were not retrieved from the database search were also added to the results.

After deduplication, titles and abstracts were reviewed to identify articles that met our inclusion criteria: Articles had to relate to an infectious disease, they had to describe an investigation of an outbreak (as defined above) and they had to involve application of spatial analysis or mapping. Abstracts that did not include clear information on the inclusion criteria were brought forward for full-text review. Full texts of articles were assessed with the same inclusion criteria.

We then ran a search of the same databases using only the outbreak investigation terms. We simulated the deduplication and screening process that would result from this search by excluding the same proportion of articles at each step as in the original search. This allowed us to obtain a crude estimate of the total number of published reports of infectious disease outbreak investigations and therefore the proportion that used spatial methods.

Data extraction

Each included study was reviewed and information about the spatial methods and outcomes of the studies extracted (Table 1). Descriptive details obtained

Table 1a

Details of included studies, systematic literature review on spatial methods in infectious disease outbreak investigations (n = 80)

Reference	Infectious disease	Location	Publication year	Context	Prospective/ retrospective	Spatial methods used	Stage of investigation[a]	Outcome summary
Acheson [44]	Syphilis	United Kingdom	2011	Sexual transmission	P	Dot map; rate map	4, 7	Some clusters found in high deprivation areas; adverts placed on social networks linked to users' postcodes
Boccia [67]	Salmonellosis	United Kingdom	2004	Food	P	Dot map; spatial case definition; source proximity	3, 4, 5	No significant difference between closest case and control to suspect outlets
Carr [59]	Legionnaires' disease	United Kingdom	2010	Environmental	P	Dot map; case movement map; spatial case definition	3, 4	Identified no hot spots; concluded pseudo-cluster
Hyland [47]	Legionnaires' disease	United Kingdom	2008	Environmental	P	Dot map; case movement map; spatial case definition	3, 4, 5, 6, 7, 8	Sullage tanks identified as source; review of national guidelines
Keramarou [26]	Legionnaires' disease	United Kingdom	2010	Environmental	P	Dot map; case movement map; spatial case definition	3, 4	Two distinct spatiotemporal clusters identified but no definitive source
Kirrage [40]	Legionnaires' disease	United Kingdom	2007	Environmental	P	Dot map; case movement map; spatial case definition; source proximity	3, 4, 5, 7	Identified cluster of cooling towers as likely source; closed and cleaned one of the towers
Neira-Munoz [68]	Cryptosporidiosis	United Kingdom	2007	Water	P	Dot map; thematic map; spatial case definition	3, 4, 6	Hypothesis that low level contamination of drinking water caused outbreak; potential change in water monitoring suggested
Sanson [69]	Foot and mouth disease	United Kingdom	2011	Farm	R	Dot map; spatial case definition; source proximity; case–case distance; air dispersion modelling	5, 6	Distance and direction from index farm significant predictors of infection status; minimum infective dose might be less than previously established
Wallensten [33]	Q fever	United Kingdom	2010	Farm	P	Dot map; spatial case definition; air dispersion modelling	3, 4, 5	Air from each of suspected farms may have exposed town, couldn't rule any out as potential sources
Le Comber [34]	Cholera & malaria	United Kingdom & Egypt	2011	Vector/water	R	Dot map; spatial average; geographic profiling	4, 5	Identified most likely locations of sources of infection
Manfredi Selvaggi [70]	Q fever	Italy	1996	Farm	P	Rate map; thematic map; spatial case finding	3, 4	Infected individuals tended to live closer to sheep migration route
Orsi [71]	Measles	Italy	2010	Community	P	Dot map	4	Identified worst affected areas
Varani [72]	Leishmaniasis	Italy	2013	Vector	P	Dot map	3, 4	Most patients in hilly, rural areas
Norstrom [31]	Acute respiratory disease	Norway	1999	Farm	R	Dot map; smoothed incidence map; spatial case definition; space-time scan statistic; k-nearest neighbour test; Knox test	3, 4, 5	Described progression of outbreak; identified cluster; supports hypothesis of single common source of infection
Nygard [32]	Legionnaires' disease	Norway	2008	Environmental	P	Dot map; case movement map; spatial case definition; source proximity; air dispersion modelling	3, 4, 5, 6, 7	Identified industrial air scrubber as source of outbreak; scrubber closed, new routines for cleaning and national regulations implemented

MMR: measles-mumps-rubella vaccine; NA: not available; P: prospective; R: retrospective; SARS: severe acute respiratory syndrome.

[a] Stages in outbreak investigations defined as: 1. Establishing existence of an outbreak; 2. Confirming diagnosis; 3. Defining and identifying outbreak cases; 4. Describing cases and developing hypotheses; 5. Evaluating hypotheses and drawing conclusions; 6. Comparing with established facts; 7. Executing prevention measures; 8. Communicating findings.

Table 1b

Details of included studies, systematic literature review on spatial methods in infectious disease outbreak investigations (n = 80)

Reference	Infectious disease	Location	Publication year	Context	Prospective/ retrospective	Spatial methods used	Stage of investigation[a]	Outcome summary
Nygard [41]	Giardiasis	Norway	2006	Water	P	Dot map; thematic map; spatial case definition	3, 4, 5, 7	Higher attack rate in zone supplied by water supply A; boil water notice issued; flushed distribution system
Abellan [73]	Legionnaires' disease	Spain	2002	Environmental	R	Dot map; smoothed incidence map; k-function	4 ,5	Cases more aggregated than controls; confirmed environmental origin of outbreak
Garcia-Fulgueiras [57]	Legionnaires' disease	Spain	2003	Environmental	P	Rate map; spatial case definition; source proximity	3, 4, 5, 6	Zone of exposure around hospital associated with illness; replaced cooling tower; Legionella may be able to spread over larger distances from source than previously thought
Jansa [58]	Legionnaires' disease	Spain	2002	Environmental	P	Dot map; spatial case definition	3, 4	Cooling towers identified as source
Hackert [11]	Q fever	The Netherlands	2012	Farm	R	Dot map; smoothed incidence map; spatial case definition; source proximity	3, 4, 5, 6	Incidence increased with proximity to index farm; cases scattered in wedge shape area downwind of farm
Schimmer [74]	Q fever	The Netherlands	2010	Farm	R	Dot map; thematic map; spatial case definition; source proximity; spatial average	3, 4, 5	Gradual diminishing risk from certain farms, identified as probable sources
van der Hoek [50]	Q fever	The Netherlands	2012	Farm	R	Dot map; rate map; thematic map; smoothed incidence map; source proximity	4, 8	Identified 5 hot spots, all around infected dairy goat farms
Gubbels [42]	Campylobacteriosis	Denmark	2012	Water	P	Dot map; thematic map; spatial case definition	3, 4, 7	Cases lived across entire water supply area; concluded contamination of central water supply; implemented boiling order
Nguyen [63]	Legionnaires' disease	France	2006	Environmental	P	Dot map; rate map; case movement map; spatial case definition; spatial case finding; air dispersion modelling	3, 4	Dispersion of plumes from cooling tower correlated with geographical distribution of cases; spread over longer distance than previously thought possible
Kistemann [29]	Salmonellosis	Germany	2000	Hospital	P	Thematic maps; schematic map; spatial case definition	1, 3, 4, 7, 8	Identified functional relationship between cases; measures introduced to prevent future outbreaks
Fitzpatrick [28]	Measles	Ireland	2012	Community	P	Dot map; thematic map	4, 7	Identified emergence of cluster during outbreak in real time; intervention in high rate area - expediated MMR vaccine schedule/ catch-up campaign
Ulugtekin [18]	Measles	Turkey	2007	Community	P	Dot map; thematic maps	4	Identified high incidence areas

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[a] Stages in outbreak investigations defined as: 1. Establishing existence of an outbreak; 2. Confirming diagnosis; 3. Defining and identifying outbreak cases; 4. Describing cases and developing hypotheses; 5. Evaluating hypotheses and drawing conclusions; 6. Comparing with established facts; 7. Executing prevention measures; 8. Communicating findings.

Table 1c

Details of included studies, systematic literature review on spatial methods in infectious disease outbreak investigations (n = 80)

Reference	Infectious disease	Location	Publication year	Context	Prospective/ retrospective	Spatial methods used	Stage of investigation[a]	Outcome summary
Lai [75]	Influenza	Hong Kong	2010	Community	R	Dot map; smoothed incidence map; standard deviation ellipse; Moran's I; Getis-Ord Gi* statistic	4, 5	Identified hot spots and directional trend
Lai [76]	SARS	Hong Kong	2004	Community	R	Dot map; rate map; smoothed incidence map; standard deviation ellipse; origin–destination plots; Moran's I; nearest neighbour analysis	4, 5	Clear clustering identified; directional bias and radius of spread of superspreading events demonstrated
Sze-To [77]	Varicella	Hong Kong	2011	Hospital	R	Schematic map; air dispersion modelling	4, 5	Model matches epidemiological distribution of cases
Wong [39]	Influenza	Hong Kong	2010	Hospital	R	Schematic map; spatial case definition; source proximity; air dispersion modelling	3, 4, 5, 6	Proximity to air purifier associated with infection; suggests possible role for aerosol transmission
Yu [78]	SARS	Hong Kong	2005	Hospital	R	Schematic map; spatial case definition; air dispersion modelling	3, 4, 5	Attack rates higher in bays closer to index patient; suggests airborne transmission played important role
Bali [27]	Hepatitis E	India	2008	Water	P	Dot map; spatial case finding; spatial case definition	3, 4	Cases mapped to water supply distribution area
Nisha [43]	Dengue fever	India	2005	Vector	P	Dot map; spatial case finding; scan statistic	3, 4, 7	Identified cluster; fogging and larval reduction; drawing up standard protocol for GIS in outbreaks
Saha [79]	Shigellosis	India	2009	Water	P	Rate map; spatial case definition	3, 4	Incidence higher downstream of damaged pipeline
Sarkar [46]	Diarrhoea	India	2007	Water	P	Dot map; thematic map; spatial case definition; source proximity; spatial case finding; spatial scan statistic	3, 4, 5, 7, 8	Showed dispersed nature of outbreak; no significant clustering; funds released to improve drainage network
Sowmyanarayanan [56]	Hepatitis A	India	2008	Water	P	Dot map; spatial scan statistic	4, 5	Cluster not significant; outbreak generalised across area
Fang [80]	Influenza	China	2013	Community	R	Dot map; thematic map; environmental risk prediction model	4	Identified high incidence areas; predicted areas with high risk to inform future control efforts
Liang [81]	SARS	China	2007	Community	R	Rate map	4	Rate increased with distance from city centre, supported spatial quarantining of city for future outbreaks
Ali [82]	Dengue fever	Bangladesh	2003	Vector	R	Dot map; thematic map; smoothed incidence map; source proximity; spatial case finding; kriging	3, 4, 5	Clusters identified, generally closer to major hospitals; spatial association between clusters and vector populations
Tenzin [83]	Rabies	Bhutan	2010	Community	R	Dot map; spatial average; standard deviation ellipse	4	Visualised spread of outbreak; seemed to follow road network that had many free-roaming dogs

MMR: measles-mumps-rubella vaccine; NA: not available; P: prospective; R: retrospective; SARS: severe acute respiratory syndrome.

[a] Stages in outbreak investigations defined as: 1. Establishing existence of an outbreak; 2. Confirming diagnosis; 3. Defining and identifying outbreak cases; 4. Describing cases and developing hypotheses; 5. Evaluating hypotheses and drawing conclusions; 6. Comparing with established facts; 7. Executing prevention measures; 8. Communicating findings.

Table 1D

Details of included studies, systematic literature review on spatial methods in infectious disease outbreak investigations (n = 80)

Reference	Infectious disease	Location	Publication year	Context	Prospective/ retrospective	Spatial methods used	Stage of investigation[a]	Outcome summary
Nishiguchi [84]	Influenza	Japan	2009	Farm	R	Dot map; scan statistic	3, 4, 5	Identified cluster and factors associated with farms inside cluster
Siddiqui [85]	Cholera	Pakistan	2006	Water	R	Dot map; spatial case definition; k-nearest neighbour test	3, 4, 5	Clustering in one of the outbreaks investigated; water reservoir identified as likely source
Miranda [86]	Ebola	Philippines	2002	Breeding facility	R	Schematic map	4	Documented progression of outbreak
Le [87]	Porcine high fever disease	Vietnam	2012	Farm	R	Dot map; smoothed incidence map; spatial and space–time scan statistic; k-nearest neighbour test; Knox test; space–time k function	4, 5	Little evidence for clustering; thought not to be important in this outbreak
Addiss [88]	Legionnaires' disease	United States	1989	Environmental	P	Dot maps; spatial case definition; source proximity	3, 4, 5	Rate decreased with distance from one cooling tower; implicated as probable source of outbreak
Blondin [89]	Blastomycosis	United States	2007	Environmental	R	Dot map; thematic map; source proximity	4, 5	No common source identified; infection likely to have been acquired close to homes
Brown [60]	Legionnaires' disease	United States	1999	Environmental	P	Dot map; thematic map; spatial case definition; source proximity	3, 4, 5	Transmission mostly in close proximity to cooling towers
Chung [90]	West Nile fever	United States	2013	Vector	R	Dot map; rate map; Getis-Ord Gi* statistic	4, 5	As outbreak progressed it became clustered and hot spot was identified
McKee [36]	Shigellosis	United States	2000	Water	P	Dot map; k-nearest neighbour test	4, 7	Space–time clustering found; identified communal wading pools as probable source; targeted information campaigns and education
Mongoh [91]	Anthrax	United States	2008	Farm	R	Dot map; thematic map	4	Displayed spatial distribution of premises with cases n study
Pfister [92]	Blastomycosis	United States	2011	Environmental	P	Dot map; spatial case definition; spatial average	3, 4	Centre of outbreak identified, north of river; yard waste disposal identified as likely source
Roy [25]	Blastomycosis	United States	2013	Environmental	P	Dot map; spatial case definition; scan statistic	1, 3, 4	Confirmed the presence of the outbreak
Bowie [93]	Toxoplasmosis	Canada	1997	Water	P	Dot map; thematic map	4, 5	Outbreak-related cases in area served by water distribution system
Epp [94]	Anthrax	Canada	2010	Farm	R	Thematic map; smoothed incidence map; velocity vector map; spatial case definition; space time scan statistic; k-nearest neighbour test; k-function; Oden's Ipop	4, 5	Three separate movements of spread identified; clusters located

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[a] Stages in outbreak investigations defined as: 1. Establishing existence of an outbreak; 2. Confirming diagnosis; 3. Defining and identifying outbreak cases; 4. Describing cases and developing hypotheses; 5. Evaluating hypotheses and drawing conclusions; 6. Comparing with established facts; 7. Executing prevention measures; 8. Communicating findings.

Table 1e

Details of included studies, systematic literature review on spatial methods in infectious disease outbreak investigations (n = 80)

Reference	Infectious disease	Location	Publication year	Context	Prospective/ retrospective	Spatial methods used	Stage of investigation[a]	Outcome summary
Parkinson [22]	Anthrax	Canada	2003	Farm	R	Dot map; thematic maps	4	Described physical characteristics of outbreak and documented spatial descriptive patterns
Pasma [95]	Influenza	Canada	2008	Farm	R	Thematic map; spatial average; standard deviation ellipse; k-nearest neighbour test; spatial scan statistic; Knox test; nearest neighbour analysis; Mantel's test	4, 5, 6	Identified and located clusters; outbreak established in densely populated areas, moved to less densely populated areas; suggests focus for surveillance
Morrison [96]	Dengue fever	Puerto Rico	1998	Vector	R	Dot map; Knox test; k-function analysis; Barton–David test	3, 4	Significant case clustering within households over short periods of time; but in general, cases had pattern similar to population as a whole; control measures need to be applied to entire municipality
Chadee [97]	Meningococcal meningitis	Trinidad	2006	Community	P	Dot map; case–case distance	1, 4	Revealed two clusters
Chadee [55]	Dengue fever	West Indies	2005	Vector	R	Dot map; k-nearest neighbour test	4	Cases occurred in clusters when mosquito densities were high enough
Affolabi [24]	Tuberculosis	Benin	2009	Community	R	Dot map; case movement map	1, 4	Identified potential cluster
Bartels [98]	Cholera	Ethiopia	2010	Water	P	Dot map	4	Cases mapped along river; thought to be most likely source
Luquero [49]	Cholera	Guinea-Bissau	2011	Water	P	Dot map; rate map; smooth incidence maps; spatial case finding; scan statistic; k-function	3, 4, 5, 7, 8	Two clusters identified; improved sanitation systems and hygiene collection in affected area
Rivas [23]	Influenza	Nigeria	2010	Farm	R	Dot map; thematic maps; spatial case definition; case–case distance; risk factor proximity	3, 4, 5	Supports hypothesis that major highway network promoted epidemic spread
Roquet [20]	Cholera	Senegal	1998	Water	R	Dot map; rate map	4	Identified high incidence areas
Bessong [99]	Diarrhoea	South Africa	2009	Water	P	Dot map; spatial case finding	3, 4	Identified hot spots of the outbreak; two water extraction points implicated
Fevre [35]	Trypanosomiasis	Uganda	2001	Vector	R	Dot map; spatial case definition; source proximity; spatial scan statistic	3, 4, 5	Significant cluster detected; distance from market significant risk factor
Sasaki [30]	Cholera	Zambia	2008	Water	R	Dot map; rate map; Voronoi diagram; nearest neighbour analysis; Moran's I	4, 5	Significant clustering found in areas with lower coverage of latrines and effective drainage systems
Fernandez [45]	Cholera	Zimbabwe	2011	Water	R	Dot map; thematic map; rate map; empirical Bayes smoothing	4, 5, 7	Spatial pattern linked to historical social construction of city characterised by distinct regions of socioeconomic status

MMR: measles-mumps-rubella vaccine; NA: not available; P: prospective; R: retrospective; SARS: severe acute respiratory syndrome.

[a] Stages in outbreak investigations defined as: 1. Establishing existence of an outbreak; 2. Confirming diagnosis; 3. Defining and identifying outbreak cases; 4. Describing cases and developing hypotheses; 5. Evaluating hypotheses and drawing conclusions; 6. Comparing with established facts; 7. Executing prevention measures; 8. Communicating findings.

Table 1f

Details of included studies, systematic literature review on spatial methods in infectious disease outbreak investigations (n = 80)

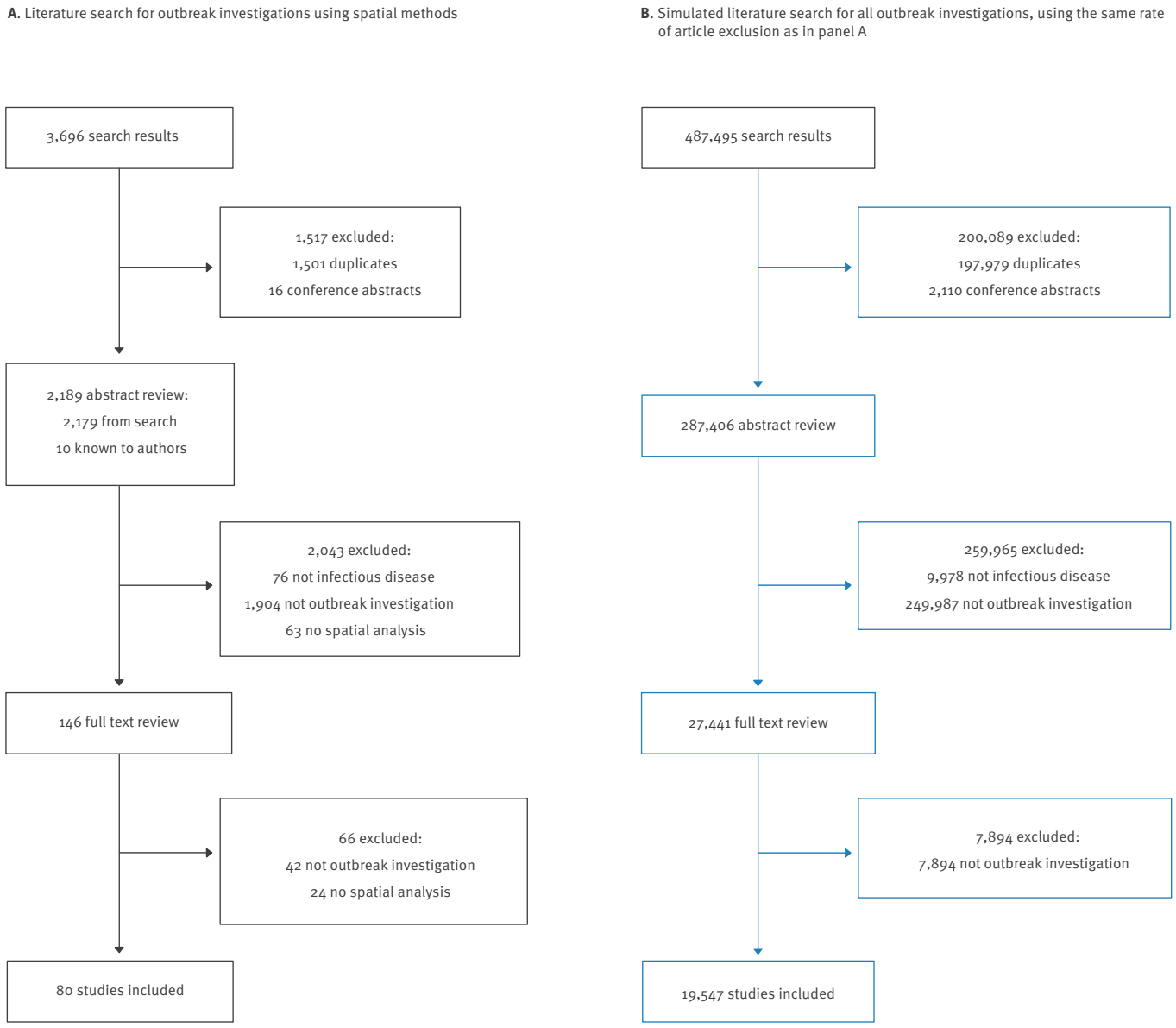
Reference	Infectious disease	Location	Publication year	Context	Prospective/ retrospective	Spatial methods used	Stage of investigation[a]	Outcome summary
Angulo [100]	Variola minor	Brazil	1979	Community	R	Dot map; smoothed incidence map	4	Demonstrated importance of schools in epidemic spread
Barcellos [21]	Leptospirosis	Brazil	2000	Water	R	Dot map; thematic maps; risk factor proximity	4	Concentration of cases observed; identified characteristics of areas
Barreto [19]	Schistosomiasis	Brazil	1993	Vector	P	Dot map; thematic maps	4	Children with frequent water contact around open bodies of water, no sewage disposal, absence of water supply associated with infection
de Moura [101]	Toxoplasmosis	Brazil	2006	Water	P	Dot map; rate map	4, 6, 7	Cases more likely to be served by water reservoir A than B; closed reservoir.
Passos [102]	Rabies	Brazil	1998	Community	R	Dot map	4	Cases corresponded to parts of city with most slums and lower income populations
Rotela [48]	Dengue fever	Argentina	2007	Vector	R	Dot map; smoothed incidence map; Knox test; environmental risk prediction model	4, 5	Identified clusters and developed predictive risk model
Rivas [103]	Foot and mouth disease	Uruguay	2003	Farm	R	Dot map; thematic map; source proximity	4, 5	Generated hypothesis that early epidemic virus disseminated took advantage of road network, then spread outwards
Firestone [104]	Influenza	Australia	2011	Farm	R	Dot map; smoothed incidence map; spatial social network analysis; space-time scan statistic; kriging	4, 5, 6	Local spread through contact network to distance of 15 km; identified 5 significant clusters
Waldron [105]	Cryptosporidiosis	Australia	2011	Water	R	Dot map	4	Identified hot spots and movement of cluster over time
White [38]	Legionnaires' disease	New Zealand	2013	Environmental	P	Dot map; thematic map; scan statistic; Moran's I	4, 5, 6, 8	Identified clusters; case distribution consistent with plume effect from probable source
Turcios-Ruiz [106]	Necrotising enterocolitis	NA	2008	Hospital	P	Schematic map; spatial case definition; Grimson test	3, 4, 5	Clustering identified; suggested possible association with caregivers working in affected area

MMR: measles-mumps-rubella vaccine; NA: not available; P: prospective; R: retrospective; SARS: severe acute respiratory syndrome.

[a] Stages in outbreak investigations defined as: 1. Establishing existence of an outbreak; 2. Confirming diagnosis; 3. Defining and identifying outbreak cases; 4. Describing cases and developing hypotheses; 5. Evaluating hypotheses and drawing conclusions; 6. Comparing with established facts; 7. Executing prevention measures; 8. Communicating findings.

Figure 2

Study selection, systematic literature review on spatial methods in infectious disease outbreak investigations (n = 3,696)



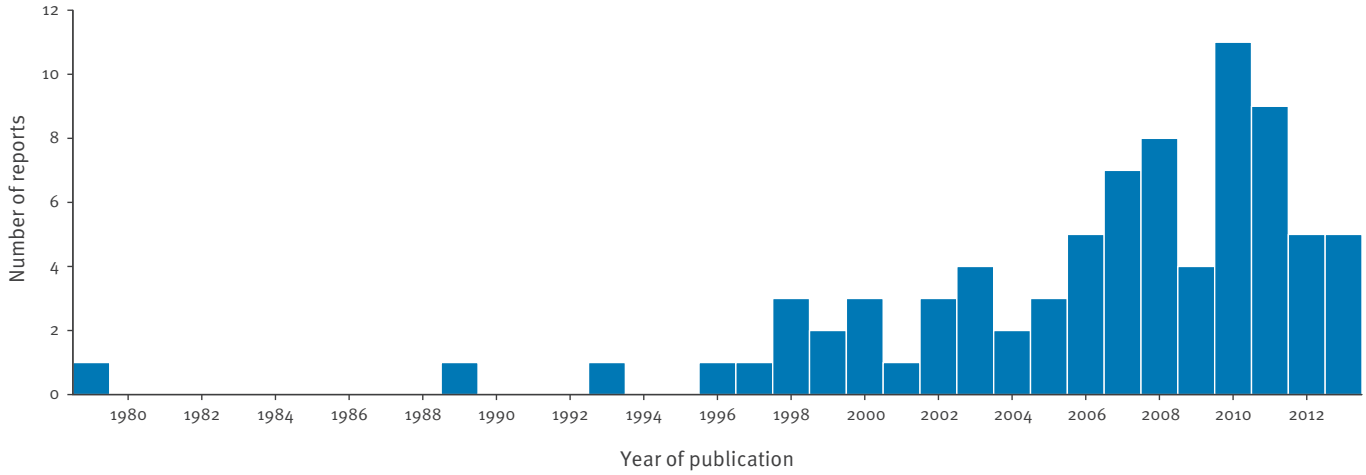
Blue boxes are estimated numbers. Key details of all 80 included articles are described in Table 1.

were the location of the outbreak, date of publication, type of infection, context or suspected source, and whether the study was prospective or retrospective. Methodological details were the type of spatial methods used and the tools employed. Outcomes were results of the investigations that related specifically to the use of spatial methods and any comments on their advantages or limitations. We summarised reports according to the date of publication, type of infection, location and context of the outbreak. Spatial methods used were categorised into four broad classes: visualisation, cluster analysis, modelling and other spatial analyses.

To demonstrate the utility of spatial methods during outbreak investigations, and therefore how they could be used in the future, we identified the stage(s) of the investigation to which they were applied. Outbreak investigations can be delineated into steps in various ways, and for the purpose of this review we used the following steps, adapted from the ECDC's Field Epidemiology Manual [17]: 1. Establishing existence of an outbreak, 2. confirming diagnosis, 3. defining and identifying outbreak cases, 4. describing cases and developing hypotheses, 5. evaluating hypotheses and drawing conclusions, 6. comparing with established facts, 7. executing prevention measures, 8. communicating findings.

Figure 3

Reports of outbreak investigations using spatial methods (n = 80)



Results

Article screening and estimation of proportion with spatial methods

After excluding duplicates, we identified a total of 2,189 articles for abstract screening. Of these, 146 were selected for full text review and 80 of them were included in the analysis. Reasons for article exclusion are summarised in Figure 2A. Conducting the search without any terms specific to spatial analysis identified 487,495 articles. Assuming the same rate of article exclusion at each step in the review process, we estimated the total number of published articles relating to outbreak investigations of infectious diseases at ca 20,000 (Figure 2B). The overall proportion of published outbreak investigation reports that explicitly described spatial methods was therefore around 0.4%.

Characteristics of studies included

Publication of outbreak investigations with spatial methods has increased markedly since 2000, with over half (n = 42) of the studies published since 2008 (Figure 3). Most articles (n = 66; 83%) concerned infections in human populations, of which the most frequently investigated infections were Legionnaires' disease (n = 12), cholera (n = 7) and influenza (n = 7) (Table 2). Correspondingly, the most common transmission contexts for human infections were water/sanitation (n = 20), followed by environmental (n = 14) and community (n = 10) (Table 3).

Healthcare-associated infections were reported in five of the articles while food-borne and sexually transmitted infections were reported once apiece. Veterinary infections were almost exclusively linked to farms or other breeding facilities (n = 12) and influenza was the most frequently investigated infection affecting animals (n = 4). Prospective outbreak investigations comprised around half (n = 39) of the articles included, with the remainder describing retrospective analyses of outbreak data.

Figure 4 displays the outbreaks by country, with the most reports in the United Kingdom (UK) (n = 10) or the United States (US) (n = 8), and by continent, with a third of reports in Europe (n = 27) and fewer in Africa (n = 10).

Spatial methods

Spatial methods used are listed and classified according to type in Table 4.

All articles presented or referred to at least one method of visualising case distributions to describe outbreaks in space. Plotting cases as dots on a map is the simplest form of visualisation and was used in the majority (n = 68; 85%) of studies. Dot maps were either presented using case locations only, or were enhanced with further information such as their vaccination status [18], migratory status [19] or date of disease onset [20]. Thematic maps provide context to case locations by displaying the spatial distributions of other variables. Such maps were used in 25 studies and variables plotted included socioeconomic status [21], soil type [22] and road density [23]. Maps of disease rates were used in 14 studies, with data usually aggregated according to administrative boundaries. Smoothed incidence maps were used in 13 studies. Other methods for visualising outbreaks that were used in fewer studies included standard deviation ellipses and velocity vector maps. Both use the locations of cases to describe the direction of spread of outbreaks.

Cluster analyses were used in 24 studies (30%), and spatial scan statistics were the most frequently used (n = 13 studies). *k*-nearest neighbour tests, *k*-function analyses and the Knox test were also used frequently (n = 7, 5 and 5 studies, respectively). Modelling approaches were used in 13 studies, including seven which used air dispersion models to identify areas that

Table 2

Infectious diseases investigated by category (n = 80 reports)

Infection category	n	Infection	n[a]	References
Respiratory	23	Legionnaires' disease	12	[26,32,38,40,47,57-60,63,73,88]
		Influenza	7	[23,39,75,80,84,95,104]
		SARS	3	[76,78,81]
		Acute respiratory disease	1	[31]
Intestinal	18	Cholera	7	[20,30,34,45,49,85,98]
		Cryptosporidiosis	2	[68,105]
		Diarrhoea	2	[46,99]
		Salmonellosis	2	[29,67]
		Shigellosis	2	[36,79]
		Campylobacteriosis	1	[42]
		Giardiasis	1	[41]
		Necrotising enterocolitis	1	[106]
Viral haemorrhagic fever	8	Dengue fever	5	[43,48,55,82,96]
		Ebola	1	[86]
		Porcine high fever disease	1	[87]
		West Nile fever	1	[90]
Viral skin infections	7	Measles	3	[18,28,71]
		Foot and mouth disease	2	[69,103]
		Varicella	1	[77]
		Variola minor	1	[100]
Protozoal	5	Toxoplasmosis	2	[93,101]
		Leishmaniasis	1	[72]
		Malaria	1	[34]
		Trypanosomiasis	1	[35]
Rickettsioses	5	Q fever	5	[11,33,50,70,74]
Bacterial zoonotic	4	Anthrax	3	[22,91,94]
		Leptospirosis	1	[21]
Mycoses	3	Blastomycosis	3	[25,89,92]
Viral CNS infections	2	Rabies	2	[83,102]
Viral hepatitis	2	Hepatitis A	1	[56]
		Hepatitis E	1	[27]
Helminthiases	1	Schistosomiasis	1	[19]
Other bacterial	1	Meningococcal meningitis	1	[97]
Sexually transmitted	1	Syphilis	1	[44]
Tuberculosis	1	Tuberculosis	1	[24]

CNS: central nervous system; SARS: severe acute respiratory syndrome.

[a] The total is 81 because one study reported two investigations.

may have been exposed to air from suspected contaminated environmental sources.

A range of other spatial methods based on geographic attributes of cases were also identified. These included methods for defining (n = 31 studies) and identifying (n = 8 studies) cases, summarising the average locations of cases (n = 5 studies) and assessing proximity to potential sources (n = 16 studies).

Analytic methods were used less frequently in prospective than retrospective articles: Cluster methods were used in 16 (39%) retrospective compared with eight (21%) prospective studies, and modelling in 10 (24%) and three (8%) retrospective and prospective analyses, respectively.

The most frequently cited GIS software was ArcGIS/ArcView, used in 30 studies, with MapInfo the other commonly used programme (n = 7). Various other packages including R, ClusterSeer, GeoDa and SaTScan were used for specific analyses.

Application of spatial methods in outbreak investigations

Applications of spatial methods to different stages during outbreak investigations are described below (see also Table 1).

1. Establishing existence of an outbreak

Few studies (n = 4) used spatial methods to assist with establishing the existence of an outbreak. Methods that were used aimed to identify unusual patterns of cases, either visually or through formal statistical tests of clustering.

For example, Affolabi and colleagues described complementary use of molecular and geographic methods to identify an outbreak of tuberculosis in Benin [24]. Among a series of 194 *M. tuberculosis* isolates, 17 belonged to the Beijing genotype and exhibited an identical 12-loci subtype. Mapping of patients' residences, workplaces and movements revealed a corresponding spatial cluster, confirming that the cases were likely to be linked. In another study, Roy and colleagues plotted the locations of cases of blastomycosis in Wisconsin after noting an increase in the number of reports [25]. They visually identified clustering within five neighbourhoods and used the spatiotemporal scan statistic to confirm that this was statistically significant.

2. Confirming diagnosis

Although knowledge of the endemicity of diseases in the geographic regions in which outbreaks arise is useful in developing plausible preliminary diagnostic hypotheses, spatial methods alone are not able to confirm a diagnosis and were therefore not used for this purpose in any of the studies.

3. Defining and identifying outbreak cases

Geographic boundaries in which outbreak cases were defined were stated explicitly in over a third (n = 31) of the studies. For instance, Keramarou and colleagues' investigation of an outbreak of Legionnaires' disease included only cases that lived or worked in the outbreak area, defined as a 12 km corridor on either side of a major road [26].

Table 3

Contexts of outbreak investigations of human and animal diseases (n = 80 reports)

Context	Human[a]		Animal	
	n	References	n	References
Water/sanitation	20	[20,21,27,30,34,36,41,42,45,46, 49,56,68,79,85, 93,98,99,101,105]	0	
Environmental	14	[25,26,32,38,40,47,57-60,63,73,88,92]	1	[89]
Community	10	[18,24,28,71,75,76,80,81,97,100]	2	[83,102]
Vector-borne	10	[19,34,35,43,48,55,72,82,90,96]	0	
Farm/breeding facility	5	[11,33,50,70,74]	12	[22,23,31,69,84,86,87, 91,94,95,103,104]
Healthcare-associated	5	[29,39,77,78,106]	0	
Food	1	[67]	0	
Sexually transmitted	1	[44]	0	
Total [b]	**66**		**15**	

[a] Includes outbreaks affecting humans that had animal origin.

[b] The total is 81 because one article reported two investigations.

Spatial methods were also used to assist with active case finding in eight studies. Bali and colleagues describe a search for cases of hepatitis E prompted by identification of three cases in a small town in northern India [27]. A house-to-house survey in this region identified 3,170 cases of jaundice with an attack rate of 5.2%.

4. Describing outbreak cases and developing hypotheses

Use of dot mapping to support an outbreak in real time is described by Fitzpatrick and colleagues, who investigated a rise in measles cases in Dublin, Ireland [28]. Continuously updating their maps throughout the outbreak allowed them to identify clustering of cases as soon as it developed and ultimately assisted with targeting of control interventions.

Simple maps were also used to develop hypotheses about the origins of outbreaks. For example, Kistemann and colleagues plotted cases by date of onset in an investigation of a nosocomial *Salmonella* outbreak [29]. Their schematic map revealed the central kitchen as the only functional relationship linking the cases, which they therefore hypothesised to be the source of the infection.

Sasaki and colleagues created a Voronoi diagram to demarcate their study area using locations of water taps [30]. Plotting incidence rates in the different areas defined by these water tap boundaries helped to visualise clear spatial clustering of cholera cases associated with poor water and sanitation facilities. Smoothed incidence maps were used in an investigation by Norström and colleagues into acute respiratory disease in Norwegian cattle herds. They used smoothing based on kernel density estimation to describe the progression of the outbreak, which was shown to spread locally before jumping to new areas [31].

A common method to develop hypotheses about sources of infections was to construct concentric circles of varying radii around potential sources and compare the attack rates in each. Nygard and colleagues used this technique in an investigation of Legionnaires' disease in Norway [32]. They calculated attack rates in five rings of increasing distance around eight potential sources and observed a trend of decreasing rate ratios with increasing distance from an air scrubber. Other metrics used to describe cases included calculating their average location and proximity to risk factors.

Possible air-borne spread of Q fever from farms near Cheltenham, UK was investigated by Wallensten and colleagues using the Numerical Atmospheric-dispersion Modelling Environment (NAME) model [33]. Plotting the modelled distribution showed that air from each of the suspected farms may have exposed the town. Geographic profiling is another modelling technique used to generate hypotheses about the locations of sources of infections. Le Comber and colleagues used this method to identify most likely locations of mosquito breeding sites using residential locations of a series of cases of malaria in Cairo, Egypt [34].

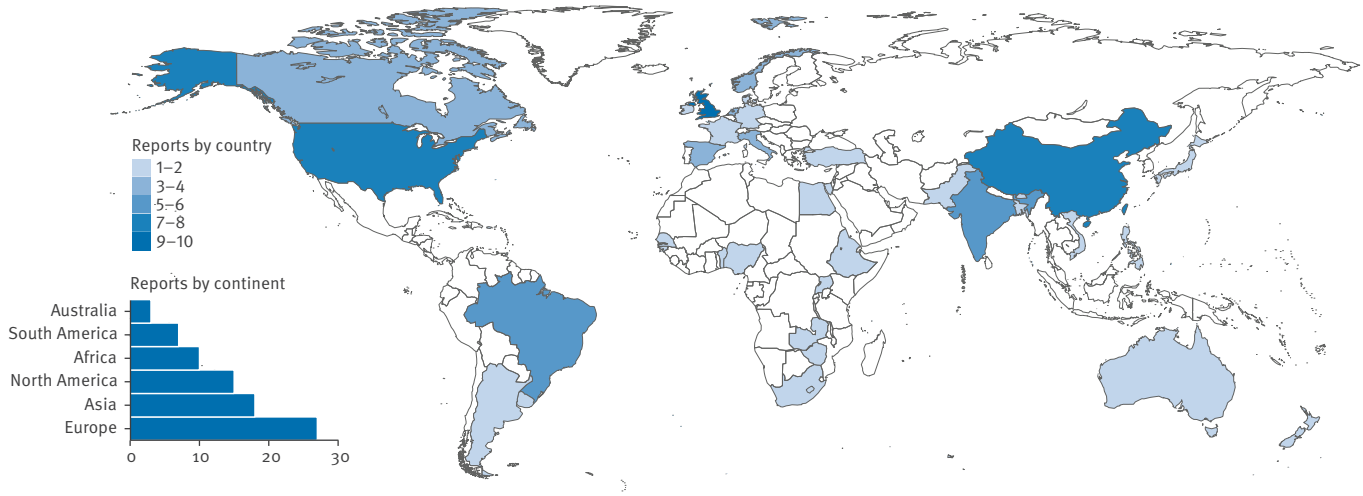
5. Evaluating hypotheses and drawing conclusions

More than half of the studies (n = 42) used statistical tests, such as cluster and regression analyses, to conduct formal evaluations of hypotheses arising from observations of case distributions. Fevre and colleagues, for example, assessed clustering of cases of trypanosomiasis under the hypothesis that a cattle market was the source of the outbreak [35]. A significant cluster encompassing the location of the market was detected using the spatiotemporal scan statistic, supporting this theory.

In an investigation on a military installation in North Carolina, McKee and colleagues used the *k*-nearest

Figure 4

Locations of outbreak investigations using spatial methods by country and continent (n = 80)



neighbour method to identify significant spatiotemporal clustering of shigellosis [36]. They used dot maps to locate the area with intense transmission and targeted it with educational interventions to bring the outbreak under control.

Combinations of multiple tests for clustering were used in some studies, such as Norström and colleagues' investigation of acute respiratory disease in Norwegian cattle herds [31]. They combined the Knox test [37], a global test for space–time clustering, with the *k*-nearest neighbour test and space–time scan statistic. These tests allowed them, respectively, to define the smallest distance and time frame in which the events had been clustered, to determine whether cases tended to be close to other cases and to locate the most significant clusters. All methods indicated presence of space–time clustering, adding weight to the conclusion that a common contagious source was responsible for the outbreak.

The hypothesis that risk of infection decreased with increasing distance from a suspected source was tested in several studies through regression analysis. Hackert and colleagues, for example, used linear regression of log-transformed attack rates to assess a cluster of human cases of Q fever in the Netherlands [11]. Incidence increased by a statistically significant exposure–response gradient with proximity to a dairy goat farm, which they concluded was likely to be the primary and sole source.

6. Comparing results with established facts

Results from spatial analyses in some cases provided updates to knowledge about the dynamics of the infectious agents concerned, such as their minimum infective dose and mode of transmission. For example, in an outbreak of Legionnaires' disease in Christchurch, New Zealand, cases were identified at a distance of 12 km from the implicated cooling tower [38]. White and colleagues therefore proposed updates to World Health Organization guidelines which at the time placed the area at risk from such sources at 3.2 km.

Wong and colleagues used a computational fluid dynamics model to study the spread of an influenza outbreak in a hospital setting [39]. Concentrations of hypothetical virus-laden particles from modelled air distributions correlated closely with locations of infected patients. This suggested a possible role for aerosol transmission of influenza, which is predominantly associated with transmission by droplets and direct contact.

7. Executing prevention measures

Spatially targeted interventions to control the outbreak or prevent future cases were described in many studies. Measures that aimed to control outbreaks included cleaning implicated cooling towers [40], issuing water boiling orders to areas served by contaminated supplies [41,42], vaccination catch-up campaigns [28], removal of breeding sites for mosquito larvae [43] and targeted information campaigns [36]. For example, Acheson and colleagues placed postcode-targeted information on social networks during an outbreak of heterosexually acquired syphilis in Teesside, UK [44].

Attempts to prevent future outbreaks included improvement of infrastructure [45,46], change of policy [29,32,47] and generation of risk maps [48]. Luquero and colleagues, for instance, used results of their analysis to recommend specific regions in which to focus preparedness activities to avoid future cholera outbreaks in Guinea-Bissau [49].

8. Communicating findings

All studies in this review had, by definition, used their spatial analyses in communication of findings through reports in peer-reviewed publications. Several studies also highlighted the usefulness of maps in reports or

Table 4

Spatial methods used in outbreak investigations (n = 80)

Method category	n (prospective, retrospective)	Method	n	References
Visualisation	80 (39, 41)	Dot map	68	[11,18-28,30-36,38,40-50,55,56,58-60, 63,67-69,71-76,80,82-85,87-93,96-105]
		Thematic map	25	[18,19,21-23,28,29,38,41,42,45,46,50, 60,68,70,74,80,82,89,91,93-95,103]
		Rate map	14	[20,30,44,45,49,50,57,63,70,76,79,81, 90,101]
		Smoothed incidence map	13	[11,31,48-50,73,75,76,82,87,94,100,104]
		Case movement map	7	[24,26,32,40,47,59,63]
		Schematic map	6	[29,39,77,78,86,106]
		Standard deviation ellipse	4	[75,76,83,95]
		Origin–destination plot	1	[76]
		Velocity vector map	1	[94]
		Voronoi diagram	1	[30]
Spatial exploration	47 (28, 19)	Spatial case definition	32	[11,23,25-27,29,31-33,35,39-42,46,47, 57-60,63,67-69,74,78,79,85,88,92,94,106]
		Source proximity	16	[11,32,35,39,40,46,50,57,60,67,69,74, 82,88,89,103]
		Spatial case finding	8	[27,43,46,49,63,70,82,99]
		Spatial average	5	[34,74,83,92,95]
		Case–case distance	3	[23,69,97]
		Risk factor proximity	2	[21,23]
		Spatial social network analysis	1	[104]
Cluster	24 (8, 16)	Kulldorff's spatial/ spatiotemporal scan statistic	13	[25,31,35,38,43,46,49,56,84,87,94,95,104]
		Cuzick–Edwards *k*-nearest neighbour test/Jacquez's *k*-nearest neighbours for space time interaction	7	[31,36,55,85,87,94,95]
		Knox test	5	[31,48,87,95,96]
		k-function/space–time *k*-function	5	[49,73,87,94,96]
		Moran's I	4	[30,38,75,76]
		Nearest neighbour analysis	3	[30,76,95]
		Getis Ord G*i*(*d*) statistic	2	[75,90]
		Barton–David's test	1	[96]
		Grimson test	1	[106]
		Oden's Ipop	1	[94]
		Mantel's test	1	[95]
Spatial modelling	13 (3, 10)	Air dispersion modelling	7	[32,33,39,63,69,77,78]
		Environmental risk prediction model	2	[48,80]
		Kriging	2	[82,104]
		Empirical Bayes smoothing	1	[45]
		Geographic profiling	1	[34]

presentations to communicate results to health officials [29,47], policymakers [49,50] and the public [38]. Sarkar and colleagues, for example, presented dot maps of cases of acute diarrhoeal disease in a village in southern India to the local community and health authorities [46]. Their maps visualised the proximity of cases to a contaminated water supply, and the presentation resulted in release of funds to improve sanitation in the area.

Discussion

In this review, we have identified 80 published articles of infectious disease outbreak investigations that used spatial methods, less than half a per cent of our estimated total of 20,000 outbreak reports. Although the simple dot map was the most commonly used method, a wide range of techniques were applied, including more sophisticated data visualisations and analytic tools. Across the range of studies, there were examples of spatial tools being usefully applied throughout the course of an outbreak investigation; from initial confirmation of the outbreak to describing and analysing

Table 5

Application of spatial methods to steps in outbreak investigation

1. Establish the existence of an outbreak	• Visualise case distribution (e.g. dot map) • Identify and confirm clustering (e.g. spatial scan statistic)
2. Confirm diagnosis	• Spatial methods alone cannot confirm diagnoses. Consider spatial epidemiology of infection to develop preliminary diagnostic hypotheses.
3. Define and identify outbreak cases	• Set geographic limits in which cases are considered part of the outbreak (e.g. postcode area hospital ward) • Select controls in case–control study based on same geographic limits • Use maps to assist with active case finding
4. Describe cases and develop hypotheses	• Visualise distribution of cases in relation to known risk factors or potential sources (e.g. rate map, thematic maps) • Describe progression of outbreak (e.g. dot maps at different stages, standard deviation ellipse) • Identify centre of outbreak (e.g. spatial mean) • Identify high-risk areas (e.g. attack rates in zones at different distances from potential sources) • Assess likelihood of potential sources (e.g. geographic profiling)
5. Evaluate hypotheses and draw conclusions	• Test for overall clustering (e.g. k-nearest neighbour test) • Locate significant clusters (e.g. spatial scan statistic) • Identify significant trends in attack rates with distance from potential sources (e.g. linear regression of log-transformed attack rates)
6. Compare with established facts	• Calculate maximum dispersal distance from probable source to cases • Model concentrations of infected particles to understand transmission dynamics (e.g. computational fluid dynamics, NAME atmospheric modelling)
7. Execute prevention measures	• Spatial targeting of interventions to control outbreak (e.g. order to boil water in area served by contaminated reservoir) • Spatial targeting of health promotion campaigns (e.g. using postcodes on social networks) • Identify geographic areas at risk of future outbreaks (e.g. risk mapping)
8. Communicate findings	• Use maps to communicate results to health officials/policymakers, to the public and in scientific journals

cases and communicating findings. Spatial techniques often provided valuable insights that supplemented traditional epidemiological analyses of person and time and led to public health actions.

Outbreak investigations of infectious diseases occurring in any context were included in this study. Thus, we extended the scope of two previous reviews that focused, respectively, on use of spatial methods in outbreaks of Legionnaires' disease [10] and on spatiotemporal methods to investigate transmission of infections in hospital settings [51]. In doing so, we have highlighted imbalances in application of spatial methods in different types of investigations. For example, it was notable that only one study reported an outbreak of food-borne illness. Annual summary statistics from 2013 report a total of 5,196 food- and waterborne outbreaks in the European Union (EU) [52] and 831 reports of food-borne outbreaks in 2012 in the US [53]. Although only a small proportion of these are likely to have been published in academic journals, this still indicates a substantial shortfall in use of spatial methods in this context.

Our review also allowed assessment of the extent to which spatial methods have been used in Europe. Although there was a large number of reports from Europe compared with other parts of the world, those reports derived from only 10 counties. These were predominantly in western Europe, with one report from Turkey the only investigation in eastern areas. Sharing expertise through the European Centre of Disease Prevention and Control could help to reduce this gap and strengthen outbreak investigation capacity across the continent. Expanding the use of these tools is also important in other parts of the world. Only 10 reports described outbreaks in Africa, the same number as in the UK alone, which clearly does not correlate with the distribution of the global burden of infectious diseases.

There are several limitations of spatial methods, and barriers to their use, which may account for the unequal and under-use of these tools as identified here. Firstly, reliable spatial analyses can only be conducted with accurate location data. This can be a particular challenge in developing countries in which good quality maps of residential areas are often not available [54]. Several investigations of outbreaks in such settings conducted field surveys and used Global Positioning Systems (GPS) to accurately record patient residence or risk factor locations [30,35,43,46,55,56]. However, this is a time- and cost-intensive approach and will not always be feasible. In settings in which good quality maps of residential data are available, quality of case location data is still not assured: Errors can arise from incomplete or mistranscribed addresses, out of date GIS databases or incomplete information on potential source locations. During outbreaks of Legionnaires' disease, for example, some investigators had to conduct visual searches or make public enquiries to ascertain the locations of aerosol-producing devices because there was no central registry [26,32,40,57-60].

Simplification of case locations to static points, usually residential locations, also impacts the utility of location data. In reality, individuals can become exposed to infectious agents at any place where they spend time and, similarly, traditional census population denominators that record night-time populations are not necessarily reflective of population distributions during the day [61,62]. Although a number of studies made attempts to record case movements [24,26,32,40,47,59,63], none accounted for diurnal fluctuations in populations. Ideally, this spatial uncertainty should be accounted for in data collection, analysis and visualisation stages to improve reliability of estimates of spatial risk, and new analytic methods may be required to achieve this.

Secondly, even if reliable location data are available, presentation of information on maps can be open to misinterpretation. Dot maps, for instance, were used widely but do not take into account the geographic distribution of the underlying population and can therefore mask important trends. Similarly, patterns in aggregated data are sensitive to changes in the boundaries into which they are grouped, a phenomenon known as the modifiable aerial unit problem [9]. Presentation of data on maps fails to highlight these limitations, and relatively few prospective investigations used statistical methods to formally confirm observations identified from visual displays of data.

Thirdly, researchers may be deterred from using spatial analytic methods because they involve selection of parameter values, often with an element of subjectivity. Methods that display or identify clustering require specification of the degree to which distant points may be considered part of the same neighbourhood. For the spatial scan statistic, the user must define the maximum spatial extent of clusters in terms of the percentage of the population that can be included, in *k*-nearest neighbour analysis, the number of neighbours included must be specified, and equivalent parameters must be selected for other spatial cluster and modelling analyses [9]. Altering these parameters can have a profound influence on the results, and a trial and error approach is often required to arrive at an appropriate value. This can raise issues of multiple hypothesis testing, although some methods, including the spatial scan statistic and Tango's maximised excess events test [64], are able to adjust for this while evaluating clustering at multiple scales. Results of spatial analyses can also suffer from lack of specificity. For example, in several studies of Legionnaires' disease, spatial methods identified areas most likely to be the source of the infection, but could not discriminate between potential sources that were close together [40,57,58].

Another barrier to the effective use of spatial methods that is often cited is the expense of specialised GIS software and the need for trained personnel to operate it. Although some GIS programmes are available free of charge, the most commonly used was a commercial package, ArcGIS. However, it is also noteworthy that spatial scan statistics were the most frequently adopted analytic methods. Scan statistics can be implemented with relatively little training through SaTScan, a programme free to download from the Internet. This suggests a possible model for wider adoption of other more advanced techniques.

The results of our study point to a number of recommendations for improved practice and opportunities for further development of spatial methods. Given the potential utility of existing tools demonstrated here, under-use of these methods has doubtless resulted in missed opportunities for more effective real-time outbreak investigations. Public health officials must be supported to address this issue, and a useful first step would be development of protocols describing the application of appropriate analyses. Table 5, which relates spatial methods to specific stages in outbreak investigations, provides a framework for this. Provision of training, for example through short courses, and interdisciplinary working with specialists in geographic analysis would also be beneficial to improve the skills base of the workforce.

The majority of studies identified in this review that used analytic methods described retrospective analysis of data collected during outbreaks. These reports demonstrated the potential utility of analytic methods, but will be of greater public health benefit when used in real time. Assembly of GIS databases in advance is essential to allow spatial analyses during prospective outbreak investigations. Improving data accessibility will save time during investigations, improve accuracy of analyses and prevent duplication of effort. Reports of analyses using spatial methods would also benefit from some degree of standardisation. For example, reporting of the sources and level of precision of spatial data would enable more accurate interpretation of the results by researchers not familiar with the study site. This could be achieved, for example, through extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement with items specific to spatial data [65].

Finally, there is scope for development of new tools for analysis and visualisation of spatial data. A move towards web-based applications with user-friendly interfaces would be a natural progression, provided that these platforms included adequate training materials and data governance infrastructure. This would make spatial analyses more accessible to non-experts and could facilitate wider use of interactive displays of data and animations. The quantity and detail of geolocated data available to researchers is also increasing. GPS-enabled mobile devices and applications for self-reported or crowd-sourced information (for example *sickweather* [66], based on reports on social networks) have the potential to provide near real-time data including information on individuals' movements. Development of new analytic techniques will be needed to ensure that these data are effectively exploited and

potential benefits are met. In the context of outbreak investigations, possible applications include contact tracing and improved estimation of exposure to environmental risk factors.

The primary limitation of this study was the challenge of designing the database search strategy. Although we employed a broad search which identified a large number of abstracts for screening, the number of studies identified here will inevitably be an underestimate of the outbreak investigations that used spatial methods. Our search will not have captured studies that used spatial methods but did not refer to them explicitly in the title, abstract, subject headings or MeSH terms. Restricting the search to articles published in academic journals also excluded reports in the grey literature. Inclusion of such reports would increase the number of investigations using spatial methods, but would be unlikely to reveal novel approaches or tools not identified here. Articles published since the database search was run at the end of 2013 are also not included in this study. Recent years have seen an increase in reports using spatial methods, probably due to increased availability of GIS software. This trend is likely to have continued, and recent publications will focus on current public health issues, for example the recent Ebola outbreak in West Africa.

There was also a possible publication bias in this study: spatial analyses may have been more likely to be presented in published reports if they were found to be useful. Concerns of breaching patient confidentiality could have further limited the number of studies that published maps. Nevertheless, the proportion of studies using spatial methods was very small, and even if our estimate is an order of magnitude too low, it would still represent less than 5% of the estimated total number of investigations published.

Conclusion

Investigations of outbreaks of infectious diseases require synthesis of information and expertise from a range of fields. Spatial analyses can make many valuable contributions, with simple maps alone providing fundamental insights about the distribution of cases. However, advancements in GIS technology and increasing availability of good quality spatial data provide an opportunity for development and implementation of more sophisticated tools. Adoption of these new techniques, and wider use of existing methods, has the potential to support more effective investigations and therefore limit the public health impacts of infectious disease outbreaks.

Conflict of interest

None declared.

Authors' contributions

CS and ACH designed the study. CS did the literature search, analyses and wrote the first draft. ACH, SLC, HF, MB and SL revised and edited the final report

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