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Review

Spatial and temporal analyses to investigate infectious disease transmission within healthcare settings

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SUMMARY

Background: Healthcare-associated infections (HCAIs) cause significant morbidity and mortality worldwide, and outbreaks are often only identified after they reach high levels. A wide range of data is collected within healthcare settings; however, the extent to which this information is used to understand HCAI dynamics has not been quantified.

Aim: To examine the use of spatiotemporal analyses to identify and prevent HCAI transmission in healthcare settings, and to provide recommendations for expanding the use of these techniques.

Methods: A systematic review of the literature was undertaken, focusing on spatiotemporal examination of infectious diseases in healthcare settings. Abstracts and full-text articles were reviewed independently by two authors to determine inclusion.

Findings: In total, 146 studies met the inclusion criteria. There was considerable variation in the use of data, with surprisingly few studies (N = 22) using spatiotemporal-specific analyses to extend knowledge of HCAI transmission dynamics. The remaining 124 studies were descriptive. A modest increase in the application of statistical analyses has occurred in recent years.

Conclusion: The incorporation of spatiotemporal analysis has been limited in healthcare settings, with only 15% of studies including any such analysis. Analytical studies provided greater data on transmission dynamics and effective control interventions than studies without spatiotemporal analyses. This indicates the need for greater integration of spatiotemporal techniques into HCAI investigations, as even simple analyses provide significant improvements in the understanding of prevention over simple descriptive summaries.

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Introduction

Healthcare-associated infections (HCAIs) are problematic worldwide, with a recent report by the World Health Organization estimating hospital-wide prevalence in high-income countries at 8%. In addition to causing significant, yet preventable, morbidity and mortality in countries with centrally-funded and managed healthcare systems, such as the UK...
National Health Service, HCAIs increase waiting times and reduce availability of resources to provide care to the population. HCAIs present a unique challenge as active transmissions are often only identified after numerous patients have been infected. Additionally, the wide range of HCAI facilitators (e.g., procedures, environment) and increasingly susceptible patients complicate transmission dynamics, making prospective identification and control exceedingly difficult. When multiple cases of an infection occur within a hospital, it is difficult to differentiate a true nosocomial transmission from unrelated cases, and cohorting patients by risk group may lead to assumptions of a common source but molecular analyses often demonstrate lack of transmission.

Sophisticated spatiotemporal analyses can be used to confirm clustering statistically over time and/or space, which would increase confidence in assuming the relatedness of cases. These methods can also be used to control for the effects of cohorting and other patient characteristics that may give the spurious impression of clustering or transmission when it has not occurred. This, in turn, would provide better information on where interventions could be targeted most effectively, and when or where to anticipate outbreaks. These methods may also be useful in more rapid identification of a problem, as even small clusters (e.g. two or three cases) can be detected. Even the introduction of more simplified analytical methods to evaluate spatial and temporal relationships could be beneficial. One example is the Knox test, which has been used widely to detect time-space clusters since the 1960s. The null hypothesis in Knox testing would be that all HCAI cases are independent, and the test returns the number of pairs of cases that are deemed to cluster in time and/or space. The tool is simple to apply as it only requires information on cases, not controls or susceptible individuals, and can work on a minimal clinical dataset.

Nowadays, researchers are using geographic information systems (GIS) to further extend understanding of spatiotemporal clustering and transmission. These are computer-based programs that combine cartography, statistical analysis and database technology to layer databases on top of a predefined map. They have been applied in a range of ecological investigations of disease, and to determine whether there is a spatial association between disease risk and environmental pollution. In this study, GIS and spatial analysis were employed to investigate the risk of breast and lung cancer in a small region. After identification of significant clusters, it was possible to identify local risk factors specific to each cancer type, providing evidence of potential environmental contamination. The use of similar techniques to create hospital maps, on which infection data can be displayed and analysed, could increase understanding of local transmission and risk, and provide rapid dissemination of information through visualization.

With healthcare systems worldwide under pressure to improve patient safety whilst cutting costs, use of the existing infrastructure of routinely collected data, which are often overlooked for HCAI investigation and research, is an innovative solution. Frequently, investigations of HCAIs provide a basic epidemiological description of cases over time by providing an epidemic curve, or show how cases are distributed across wards using a diagram. However, hospital databases contain laboratory results, building management data and floor plans, and information on patient admissions and movement that could easily be incorporated into more detailed analyses to improve understanding of local HCAI epidemiology. Use of interdisciplinary tools may increase the ability to identify transmission prospectively and implement preventive measures.

The aims of this review were to determine the extent of use of spatiotemporal analyses for identifying and preventing HCAI transmission, and to provide recommendations for expanding the use of GIS and spatiotemporal statistical analyses within healthcare settings.

Methods

A systematic review of the literature on spatiotemporal examination of infectious diseases in healthcare settings between January 1961 and June 2013 was conducted using the following search terms: infection (e.g. HCAI, nosocomial, etc.); healthcare settings (e.g. hospital, intensive care, etc.); and time/space (e.g. space—time, spatial epidemiology, etc.). Potential synonyms for each search term (e.g. infection, healthcare settings and time/space) were identified and combined using Boolean operators.

To ensure comprehensive capture of the literature, BIOSIS, Cochrane Review, CSA, DARE, Embase, HEED, JSTOR, PubMed, Science Direct and Web of Science were searched for all indexed publications. Additionally, Google Scholar was searched for indexed and grey literature using the above search terms. All papers, reports, abstracts and letters were included in the initial search.

Inclusion/exclusion criteria

Inclusion/exclusion was conducted in two stages: abstract/title review and full-text review. All identified titles/abstracts were reviewed independently by two authors to ensure reliability in full-text retrieval. Papers were retrieved if they mentioned time or space in the abstract, or no abstract was provided and the title did not provide enough information to assess inclusion.

Full-text papers were reviewed independently by two authors and included if they were: (a) published post-1961; (b) written in English; (c) examined potential transmission in more than three patients; (d) provided more than a simple report of cases over time periods exceeding three months (i.e. not routine national surveillance reports); and (e) discussed time/space as a specific aim or discussion point of the study, rather than a simple mention in the results. Any studies on which the reviewers did not agree were discussed and a consensus was reached.

Data extraction

The methodologies of all included studies were reviewed and categorized into either descriptive or analytical studies of time/space, and further 'subtyped' based on the data and analyses employed. Studies were classified as 'case reporting' if they only used temporal or spatial data as an overview (i.e. an epidemic curve). ‘Basic descriptive epidemiology’ studies examined how the cases were linked by describing their locality in time and/or space and possible exposure events, but did not use statistical methods to determine the probability that they were linked. ‘Basic descriptive epidemiology with
molecular data’ studies focused on the genetic diversity of the organisms, including a description of the distribution of the strains in space and/or time. ‘Statistical spatiotemporal analysis’ studies used statistical methods to explore HCAI distribution in time or space. Studies were classified as ‘statistical spatiotemporal analysis with molecular data’ if they combined molecular data with statistical analyses to investigate the dissemination of strains across time or space. The final category, ‘spatiotemporal analysis using GIS’, included studies that used GIS within hospital settings. Findings were synthesized to evaluate the actual use of spatiotemporal analysis on infectious diseases in healthcare settings. Meta-analysis was considered but was not deemed to be feasible due to the heterogeneity of research designs and outcome measures; as such, the findings were synthesized qualitatively.

Results

In total, 43,819 titles/abstracts were identified during the literature search (Figure 1). Of these, 584 met the inclusion criteria for full-text retrieval. Four of the included studies were not available, and 146 were included in the review. Most of the studies excluded did not meet the spatiotemporal criteria; 171 provided some spatiotemporal results but did not discuss this information as it was not the focus of the study. Others examined annual trends, were case studies or review papers, or focused on non-healthcare settings. Six studies were excluded for being written in a language other than English.

Characteristics of included studies

Included studies were predominantly descriptive in their reporting of spatiotemporal data (85%), and varied greatly in encompassing a range of settings, populations and HCAs. Half of the studies were carried out hospital-wide (53%), 42% \((N = 61)\) were performed on specific wards, and only seven (5%) were based within nursing homes. The majority of studies were retrospective (72%), often using data to investigate outbreaks after the event had ended. Five (3%) studies combined retrospective analyses and prospective interventions to enhance...
surveillance, whilst the remaining 25% of studies were prospective.

Numerous HCAs were investigated, with the most common group being bacteria (62%), such as meticillin-resistant Staphylococcus aureus (MRSA) (11%) and Clostridium difficile (10%). Studies focusing solely on viral or fungal infections accounted for 29% of studies, including norovirus (3%), severe acute respiratory syndrome (3%) and Aspergillus spp. (7%). Among the 74 molecular studies in this review, only five incorporated spatiotemporal analyses to understand the transmission dynamics.

The studies were separated into two types, ‘descriptive’ and ‘analytical’, based on their use of spatiotemporal-specific statistical analyses. To enable clearer comparisons between the groups and to evaluate the variation in exploitation of clinical data, the studies were further classified into six subtypes (Table I). These are described in detail below.

Descriptive studies

Descriptive studies primarily focused on summarizing outbreak investigations, environmental assessments and cluster identification. For the vast majority of these studies, causes or sources of outbreaks, cases or clustering were the primary aim. However, simple qualitative descriptions were not sufficient in most cases to confirm or refute identified sources or clusters.

Case reporting studies

Basic descriptions of time and space were common (20%, N = 29) (Table II). Two-thirds of these studies provided a retrospective temporal description of the incidence of cases over time (i.e. an epidemic curve). Many of these studies examined outbreaks15–24 and evaluations of intervention strategies,23–25 while others attempted to identify factors associated with potential nosocomial transmission (i.e. healthcare worker carriage,26,27 direct contact with cases,28,29 inadequate cleaning of medical equipment30,31 and the physical layout of hospital utilities32,33). Only four studies described the spatial distribution of cases to show the impact of hospital renovations34 or the layout of cases across specialties,16,27,34,35 with the majority of studies describing temporal trends in cases.36,37 Most case reporting studies examined bacteria (62%); however, the most informative studies were those examining organisms such as Aspergillus spp. and Legionella spp., where environmental contamination is considered to be the primary risk factor.15,35,38–42

Basic descriptive epidemiology

Investigations that described the temporal or spatial distribution of cases were categorized as basic epidemiology (18%, N = 26) (Table II). A number of studies provided a retrospective evaluation of the incidence of cases by assessing temporal links between patients, while 58% of studies combined spatial and temporal elements to varying degrees in their evaluations. The main organisms considered were bacteria (46%); however, the studies that evaluated Aspergillus spp. focused on spatial data to the greatest extent. Indeed, the only study that focused solely on the spatial element examined fungal contamination of the hospital environment.43

Some studies combined infection information with building ‘schematics’ to explain the physical layout of the ward44 or to display the location of patients.45–51 However, these studies did not investigate the importance of the geographical distribution of cases, as has been highlighted in studies that have looked at the impact of construction on the incidence of fungal infections.43,54–56 In addition to evaluating the distribution of cases, some investigators used graphics to visualize the connections between cases,57 and attempted to identify possible clusters58–62 or provide evidence of potential transmission.63,64

A number of studies used timelines to evaluate how cases were linked.65–71 Chen et al. visualized the spread of severe acute respiratory syndrome within an emergency department.61 By combining temporal data with patient locations, the researchers identified distinct ‘clusters’ of cases, and prevented further dissemination of the disease by quarantining contacts of these individuals. Whilst the outcome was positive, the assumed clusters were based purely on description of the patients’ locations at certain times, and the lack of statistical analysis meant that the clusters were not proven to be statistically significant.

Basic descriptive epidemiology with molecular data

Most descriptive studies incorporated molecular data (47%; N = 69) (Table II), presumably because a molecular link provided more evidence of clustering or transmission than purely describing potential clusters. Numerous studies combined spatiotemporal and molecular data to attempt to develop a better understanding of strain dissemination69–71 or potential sources82–85 within the institutions in which they were conducted. Integration of molecular and temporal data enabled investigators to highlight potential links between patients, and identify potential transmission events,94–96 with greater substantiation than simple descriptive studies. In one study, researchers were able to differentiate between two consecutive outbreaks of Stenotrophomonas maltophilia on their intensive care unit by visualizing the temporal distribution of isolates identified using restriction fragment length polymorphism (RFLP)97; however, it is possible that these two distinct outbreaks could have encompassed several smaller events with the same RFLP type introduced multiple times.

Descriptive studies that included molecular data covered a range of applications including outbreak investigations,94–102 cluster identification103 and improving control interventions.104,105 However, the most common applications of

| Study type       | Study subtype                     | Number of papers (%) |
|------------------|-----------------------------------|----------------------|
| Descriptive      | Case reporting                     | 29 (20)              |
| (N = 124, 85%)   | Basic descriptive epidemiology     | 26 (18)              |
|                  | Basic descriptive epidemiology with molecular data | 69 (47) |
| Analytical       | Statistical spatiotemporal analysis | 13 (9)               |
| (N = 22, 15%)    | Statistical spatiotemporal analysis with molecular data | 5 (3) |
|                  | Spatiotemporal analysis using geographic information systems | 4 (3) |
| Temporal/space focus | First author | Year | Setting | Organism | Molecular methods | Aim | Study design |
|---------------------|--------------|------|---------|----------|------------------|-----|--------------|
| Case reporting      | Arnow PM     | 1978 | Renal ward | Aspergillus spp. | N/A | Describe outbreak | Retrospective |
|                     | Baird SF     | 2011 | Haematology ward | Non-tuberculous mycobacterium | N/A | Outbreak investigation | Retrospective |
|                     | Panwalker AP | 1986 | Whole hospital | Mycobacterium gordonae | N/A | Describe IC measures | Retrospective |
|                     | Patterson JE | 1998 | Geriatric ward | Hib | N/A | Detect clusters | Retrospective |
|                     | Addiss DG    | 1991 | Nursing home | Bordetella pertussis | N/A | Describe outbreak | Retrospective |
|                     | Alonso-Echaneve J | 2001 | Whole hospital | Mycobacterium tuberculosis | N/A | Describe outbreak | Retrospective |
|                     | Arnow PM     | 1991 | Whole hospital | Aspergillus spp. | N/A | Assess environmental contamination | Prospective |
|                     | Arnow PM     | 1998 | Haematology ward | Bloodstream infection | N/A | Describe outbreak | Retrospective |
|                     | Bayat A      | 2003 | Intensive care unit | Multiple | N/A | Describe outbreak | Retrospective |
|                     | Belani A     | 1986 | Paediatric ward | Staphylococcus aureus | N/A | Describe outbreak | Retrospective |
|                     | Bonilla HF   | 1997 | Whole hospital | VRE | N/A | Describe incidence | Prospective |
|                     | Cartmill TDI | 1994 | Haematology ward | Clostridium difficile | N/A | Describe impact of IC measures | Prospective |
|                     | Emont SL     | 1993 | Nursing home | Gastroenteritis | N/A | Describe incidence | Retrospective |
|                     | Fourneret-Vivier A | 2006 | Whole hospital | Aspergillus spp. | N/A | Describe incidence | Prospective |
|                     | Fowler SL    | 1998 | Paediatric ward | Candida lusitaniae | N/A | Describe transmission | Retrospective |
|                     | Haley CE     | 1979 | Whole hospital | Legionella pneumophila | N/A | Outbreak investigation | Both |
|                     | Klimowski LL | 1989 | Whole hospital | Aspergillus spp. | N/A | Describe incidence | Retrospective |
|                     | Lai KK       | 1998 | Whole hospital | VRE | N/A | Assess impact of IC measures | Prospective |
|                     | Larson JL    | 2003 | Whole hospital | Mycobacterium tuberculosis | N/A | Outbreak investigation | Retrospective |
|                     | Ofner-Agostini M | 2006 | Multiple hospitals | SARS | N/A | Review IC policies | Retrospective |
|                     | Pegues CF    | 2001 | Whole hospital | Aspergillus spp. | N/A | Describe incidence | Retrospective |
|                     | Abulrahia HA | 1997 | Whole hospital | Plasmodium falciparum | N/A | Determine transmission route | Prospective |
|                     | Davies BI    | 1999 | Whole hospital | Streptococcus pyogenes | N/A | Outbreak investigation | Retrospective |
|                     | Deutscher M  | 2011 | Whole hospital | Group A streptococcus | N/A | Identify risk factors | Retrospective |
|                     | Helms CM     | 1983 | Whole hospital | Legionella pneumophila | N/A | Outbreak investigation | Retrospective |
|                     | MacDonald KS | 1993 | Whole hospital | Clostridium difficile | N/A | Describe incidence | Retrospective |
|                     | McGrathEJ    | 2011 | Paediatric ward | Acinetobacter spp. | N/A | Determine transmission route | Retrospective |
|                     | WangH        | 2013 | Whole hospital | Listeria monocytogenes | N/A | Describe clinical outcomes | Retrospective |
| Basic descriptive epidemiology | Lentino JR | 1982 | Whole hospital | Aspergillus spp. | N/A | Detect clusters | Retrospective |
|                     | Bowen KE     | 1995 | Whole hospital | Clostridium difficile | N/A | Describe incidence | Retrospective |

(continued on next page)
| Temporal/spatial focus | First author | Year | Setting | Organism | Molecular methods | Aim | Study design |
|------------------------|--------------|------|---------|----------|------------------|-----|-------------|
| T Buchbinder N          | 2011         | Paediatric ward | Influenza A (H1N1) | N/A | Describe impact of IC measures | Retrospective |
| T Burney MI             | 1980         | Whole hospital  | CCHF | N/A | Outbreak investigation | Retrospective |
| T Burwen DR            | 2001         | Paediatric ward | Aspergillus spp. | N/A | Outbreak investigation | Retrospective |
| T Degail MA            | 2012         | Whole hospital  | Human metapneumovirus | N/A | Outbreak investigation | Retrospective |
| T Fretz R              | 2009         | Whole hospital  | Norovirus | N/A | Outbreak investigation | Retrospective |
| T Gastmeier P          | 2003         | Paediatric ward | Klebsiella pneumoniae | N/A | Describe a cluster of cases | Prospective |
| T Gomersall CD         | 2006         | Intensive care unit | SARS | N/A | Describe incidence | Prospective |
| T Kaplan JE            | 1982         | Nursing home  | Norovirus | N/A | Evaluate transmission | Retrospective |
| T Kimura AC            | 2005         | Paediatric ward | Ralstonia pickettii | N/A | Outbreak investigation | Retrospective |
| T Alam NK              | 2005         | Whole hospital  | Salmonella enterica | N/A | Describe cluster | Retrospective |
| T Auerbach SB          | 1992         | Nursing home  | Group A streptococcus | N/A | Outbreak investigation | Retrospective |
| T Barrett SP           | 1988         | Whole hospital  | MRSA | N/A | Describe incidence | Retrospective |
| T Bifar CM             | 1987         | Whole hospital  | MRSA | N/A | Describe outbreak | Retrospective |
| T Chen YC              | 2004         | A&E | SARS | N/A | Outbreak investigation | Retrospective |
| T Faustini A           | 2004         | Whole hospital  | Necrotizing enterocolitis | N/A | Outbreak investigation | Retrospective |
| T Foulke GE            | 1989         | Intensive care unit | Clostridium difficile | N/A | Describe use of IC measures | Retrospective |
| T Goldmann DA          | 1981         | Paediatric ward | Multiple | N/A | Describe outbreak | Prospective |
| T Lai KK               | 2001         | Transplant ward | Aspergillus spp. | N/A | Detect clusters | Retrospective |
| T Mody LR              | 2001         | Whole hospital  | Clostridium difficile | N/A | Describe incidence | Prospective |
| T Pavlov I             | 2009         | Whole hospital  | Clostridium difficile | N/A | Detect clusters | Retrospective |
| T Pegues DA            | 1993         | Nursing home  | Gastroenteritis | N/A | Outbreak investigation | Retrospective |
| T Strabelli TMV        | 2006         | Paediatric ward | Enterococcus faecalis | N/A | Detect clusters | Retrospective |
| T Turcios-Ruiz RM      | 2008         | Paediatric ward | Norovirus | N/A | Outbreak investigation | Retrospective |
| T Warren D             | 1989         | Whole hospital  | Keratoconjunctivitis | N/A | Outbreak investigation | Retrospective |

Basic descriptive epidemiology with molecular data

| S Abdallah IM          | 2006         | Whole hospital  | Multiple | RAPD | Investigate strain distribution | Retrospective |
| S Aita J               | 1996         | Whole hospital  | Mycobacterium tuberculosis | RFLP | Outbreak investigation | Retrospective |
| S Hoefnagels-Schuerman A | 1997     | Whole hospital  | MRSA | PFGE | Outbreak investigation | Prospective |
| S Katsoulidou A        | 1999         | Haematology ward | Hepatitis C virus | PCR | Outbreak investigation | Retrospective |
| S Pegues DA            | 2002         | Intensive care unit | Aspergillus spp. | RFLP | Detect clusters | Retrospective |
| S Vazquez JA           | 1993         | Whole hospital  | Candida albicans | REA | Investigate strain distribution | Prospective |
| S Venezia RA           | 1994         | Intensive care unit | Legionella pneumophila | PFGE | Identify source | Retrospective |
| S Witte W              | 2001         | Multiple hospitals | MRSA | PCR | Investigate strain distribution | Prospective |
| S Zervos MJ            | 1987         | Whole hospital  | Enterococcus faecalis | Plasmid typing | Describe incidence | Prospective |
| T Adachi JA            | 2009         | Intensive care unit | Pseudomonas aeruginosa | PFGE | Assess impact of molecular typing | Retrospective |
| T Adams G              | 1981         | Paediatric ward | Herpes simplex virus 1 | REF | Describe outbreak | Retrospective |
| Authors | Year | Setting | Pathogen | Molecular or Pathological Technique | Impact or Study Type |
|---------|------|---------|----------|-------------------------------------|---------------------|
| Alfieri N | 1999 | Intensive care unit | *Stenotrophomonas maltophilia* | RFLP | Outbreak investigation Both |
| Allander T | 1995 | Haematology ward | Hepatitis C virus | PCR/NASeq | Detect clusters Retrospective |
| Assadian O | 2002 | Paediatric ward | *Serratia marcescens* | PCR | Describe outbreak Retrospective |
| Aumeran C | 2008 | Whole hospital | VRE | PFGE | Describe use of IC measures Prospective |
| Baddour LM | 1999 | Whole hospital | *Enterococcus faecium* | CHEF | Describe outbreak Retrospective |
| Belmares J | 2009 | Whole hospital | *Clostridium difficile* | REA | Describe incidence Retrospective |
| Ben Abdeljelil J | 2011 | Paediatric ward | *Candida albicans* | PFGE | Investigate strain Retrospective |
| Ben Abdeljelil J | 2012 | Paediatric ward | *Candida albicans* | PFGE | Outbreak investigation Retrospective |
| Brillowska-Dabrowska A | 2009 | Haematology ward | *Candida parapsilosis* | RAPD | Assess impact of molecular typing Retrospective |
| DavinRegli A | 1996 | Intensive care unit | *Enterobacter aerogenes* | RAPD | Outbreak investigation Prospective |
| Eyre DW | 2012 | Multiple hospitals | *Clostridium difficile/ MRSA* | SNV analysis | Outbreak investigation Retrospective |
| Falk PS | 2000 | Burns ward | VRE | PFGE | Outbreak investigation Retrospective |
| Geis S | 2013 | Haematology ward | Respiratory syncytial virus | RT-PCR | Outbreak investigation Retrospective |
| Gray J | 2012 | Paediatric ward | *Klebsiella pneumoniae* | PFGE | Detect clusters Retrospective |
| Harvala H | 2012 | Haematology ward | Parainfluenza type 3 | RT-PCR | Outbreak investigation Retrospective |
| Helali NE | 2005 | Whole hospital | *Staphylococcus aureus* | PFGE | Outbreak investigation Both |
| Helweg-Larsen J | 1998 | Whole hospital | *Pneumocystis carinii* | PCR | Detect clusters Retrospective |
| Hong KB | 2012 | Paediatric ward | *Acinetobacter baumannii* | MLST | Outbreak investigation Retrospective |
| Kakis A | 2002 | Whole hospital | Group A streptococcus | M typing/T agglutination | Outbreak investigation Retrospective |
| Layton MC | 1993 | Dermatology ward | MRSA | PFGE | Detect clusters Retrospective |
| L'Ecuyer PB | 1996 | Multiple hospitals | *Salmonella senftenberg* | PFGE | Outbreak investigation Retrospective |
| Le Gal | 2012 | Renal ward | Pneumocystis spp. | PFGE | Detect clusters Retrospective |
| Loudon KW | 1994 | Haematology ward | *Aspergillus fumigatus* | RAPD | Detect clusters Retrospective |
| McAdams RM | 2008 | Paediatric ward | MRSA | PFGE | Detect clusters Retrospective |
| McFarland LV | 1989 | Whole hospital | *Clostridium difficile* | Immunoblot | Describe incidence Prospective |
| Peta M | 2006 | Intensive care unit | *Enterococcus faecium* | PFGE | Outbreak investigation Both |
| Rupp ME | 2001 | Paediatric ward | VRE | PFGE | Outbreak investigation Prospective |
| Sardan YC | 2004 | Whole hospital | *Klebsiella oxytoca* | AP-PCR | Outbreak investigation Retrospective |
| Zoltanski J | 2011 | Paediatric ward | ARGNB | PFGE | Describe incidence Prospective |
| and S Abb J | 2004 | Whole hospital | MRSA | PFGE | Investigate strain Prospective |
| and S Abb A | 2005 | Whole hospital | *Acinetobacter baumannii* | PFGE | Describe incidence Retrospective |
| and S Arnold KE | 2006 | Nursing home | Group A streptococcus | RFLP | Outbreak investigation Retrospective |
| and S Boyce JM | 1993 | Whole hospital | MRSA | Plasmid typing | Assess impact of IC measures Retrospective |
| and S Byers KE | 2001 | Whole hospital | VRE | PFGE | Assess impact of IC measures Prospective |
| and S Carneiro MAS | 2007 | Haematology ward | Hepatitis C virus | RT-PCR | Investigate strain Prospective |
| and S Chen LF | 2011 | Haematology ward | Influenza A (H1N1) | RT-PCR | Outbreak investigation Retrospective |
| Temporal/spatial focus | First author | Year | Setting | Organism | Molecular methods | Aim | Study design |
|------------------------|--------------|------|---------|----------|-------------------|-----|--------------|
| T and S                | Culebras E   | 2010 | Whole hospital | Acinetobacter baumannii | RAPD | Describe outbreak | Retrospective |
| T and S                | Cuny C       | 1993 | Whole hospital  | MRSA | Phage typing | Outbreak investigation | Retrospective |
| T and S                | Debast SB    | 1996 | Intensive care unit | Acinetobacter baumannii | PCR fingerprinting | Outbreak investigation | Retrospective |
| T and S                | Diab-Elschahawi M | 2012 | Intensive care unit | Candida parapsilosis | Microsatellite typing/repPCR | Outbreak investigation | Both |
| T and S                | Dijkstra L   | 1993 | Intensive care unit | Acinetobacter spp. | DNA-DNA hybridization | Investigate strain distribution | Retrospective |
| T and S                | Englund JA   | 1991 | Whole hospital | Respiratory syncytial virus | EIA | Evaluate possible transmission | Prospective |
| T and S                | Fawley WN    | 2001 | Whole hospital | Clostridium difficile | RAPD | Investigate strain distribution | Prospective |
| T and S                | Ferroni A    | 1998 | Whole hospital | Pseudomonas aeruginosa | PFGE | Outbreak investigation | Retrospective |
| T and S                | Fisher GM    | 1986 | Whole hospital | Multiple | Plasmid typing | Investigate strain distribution | Retrospective |
| T and S                | Graindorge A | 2010 | Intensive care unit | Burkholderia cenoceapica | RFLP | Describe outbreak | Retrospective |
| T and S                | Kassis C     | 2011 | Whole hospital | MRSA | PFGE | Outbreak investigation | Retrospective |
| T and S                | Kondili LA   | 2006 | Renal ward | Hepatitis B/hepatitis C | PCR | Outbreak investigation | Retrospective |
| T and S                | Levidiotou S | 2002 | Intensive care unit | Acinetobacter baumannii | RAPD | Describe outbreak | Retrospective |
| T and S                | Lin YC       | 2007 | Paediatric ward | Pseudomonas aeruginosa | PFGE | Assess HCW carriage | Retrospective |
| T and S                | Lowe C       | 2012 | Intensive care unit | Klebsiella oxytoca | PFGE | Outbreak investigation | Retrospective |
| T and S                | Lutz BD      | 2003 | Whole hospital | Aspergillus spp. | RAPD | Detect clusters | Retrospective |
| T and S                | Marx A       | 1999 | Nursing home | Gastroenteritis | RT-PCR | Determine transmission route | Retrospective |
| T and S                | Morter S     | 2011 | Whole hospital | Norovirus | Nucleic acid sequencing analysis | Outbreak investigation | Prospective |
| T and S                | Traub WH     | 1998 | Intensive care unit | Pseudomonas aeruginosa | PFGE | Investigate strain distribution | Prospective |
| T and S                | Widmer AF    | 1993 | Intensive care unit | Pseudomonas aeruginosa | CHEF | Evaluate possible transmission | Retrospective |
| T and S                | Xia Y        | 2012 | Intensive care unit | Acinetobacter baumannii | PCR | Outbreak investigation | Retrospective |
| T and S                | Yoon YK      | 2009 | Paediatric ward | VRE | PFGE | Assess impact of IC measures | Both |

S, spatial; T, temporal; N/A, not applicable; Hib, Haemophilus influenzae type B; VRE, vancomycin-resistant enterococci; SARS, severe acute respiratory syndrome; CCHF, Crimean–Congo haemorrhagic fever; MRSA, meticillin-resistant Staphylococcus aureus; ARGNB, antibiotic-resistant Gram-negative bacteria; RAPD, random amplification of polymorphic DNA; RFLP, restriction fragment length polymorphism; PFGE, pulsed-field gel electrophoresis; AP-PCR, arbitrarily primed polymerase chain reaction; repPCR, repetitive element palindromic polymerase chain reaction; CHEF, clamped homogeneous electric field electrophoresis; EIA, enzyme immunoassay; MLST, multi-locus sequence typing; PCR, polymerase chain reaction; REA, restriction endonuclease analysis; REF, restriction endonuclease fingerprinting; RT-PCR, reverse transcriptase polymerase chain reaction; A&E, accident and emergency; HCW, healthcare worker; IC, infection control; NAsEq, nucleic acid sequencing analysis; SNV, single nucleotide variant analysis.
molecular typing were in identifying the probable sources of an infection, and whether transmission had occurred. Many studies evaluated the distribution of strains over time or space, aiming to establish epidemiological links between cases, but were limited by lack of statistical analysis. The geographical layout of cases was used in some studies to suggest potential factors associated with their distribution. The study by Witte et al. mapped the distribution of MRSA strains at national level in Germany to compare changes in resistance phenotypes with various local prescription practices across regions, but there were no statistical analyses to support or refute these qualitative observations.

**Analytical studies**

Analytical studies tended to focus more on predictive modelling of future outbreaks and determining the impact of various changes within the healthcare setting, rather than describing an outbreak. They used a wide range of statistical modelling techniques, indicating a number of options for looking at spatiotemporal clustering. Interestingly, a number of the descriptive studies focused on identifying the source of an outbreak, and found that they were unable to do so conclusively. In contrast, GIS was shown to enable fast identification of possible sources during an outbreak, and enabled a targeted investigation that led to the source being discovered. This was possible using clinical data that are collected routinely, and required little additional data retrieval.

**Statistical spatiotemporal analysis**

Thirteen studies (9%) conducted statistical analyses of temporal and spatial data. All were undertaken in hospital settings, 85% (N = 11) were published in 2000 or later, and 62% (N = 8) focused on bacterial infections.

The temporal studies (N = 8) tended to be retrospective and employed time-series analysis (e.g. weekly aggregated measures plotted over time) to demonstrate if antibiotic prescription had an effect on the incidence of MRSA and *C. difficile*, or if control measures for multiple organisms reduced the incidence. Without the incorporation of temporal analysis into these investigations, the impact of the interventions may have been masked by other factors, such as seasonality. Additionally, temporal analysis was used to examine ways to improve infection control measures, while Haley and Bregman used multi-variate statistical models to assess the temporal associations between infections and overcrowding, providing evidence that handwashing compliance is reduced markedly under these conditions.

Spatiotemporal studies (N = 5) typically aimed to model infections retrospectively to investigate outbreaks and to detect clustering. By using modelling techniques, others were able to estimate the potential effect of interventions, beyond which descriptive studies could use the results to advocate their incorporation into standard control measures.

**Statistical spatiotemporal analysis with molecular data**

Only 3% (N = 5) of studies combined the use of molecular typing with spatial or temporal analyses, which has the benefit of molecular differentiation and statistical evidence in confirming transmission. All of these studies were undertaken in 2005 or later, and analysed the retrospective distribution of bacteria while attempting to establish links between isolates.

The earliest study in this category compared the effectiveness of molecular typing with spatiotemporal analysis. Polymerase chain reaction was used to characterize toxin genes in *C. difficile* isolates, which were mapped to a grid representing each ward, and analysed statistically for clustering by Knox test. This identified a single ward cluster compared with four clusters detected by molecular fingerprinting analysis, leading the investigators to conclude that the Knox test was less effective for identifying nosocomial transmission than molecular fingerprinting. However, most studies have shown that in order to gain the most from available data, spatiotemporal and molecular analyses should be used in combination.

The remaining studies evaluated potential transmission routes or attempted to gain a better understanding of outbreaks. Nuebel et al. applied whole-genome sequencing of MRSA in a neonatal intensive care unit to compare accumulated sequence variation in the isolates, and used Bayesian skyline analysis to reveal epidemiological links between patients, healthcare workers and parents. They concluded that integration of epidemiological mapping and genomic data was necessary to understand MRSA transmission. Similarly, Gandhi et al. performed a retrospective study to investigate epidemiological links between extensively-drug-resistant tuberculosis patients in South Africa by combining RFLP analysis and social network data to build transmission networks among genotypically similar patients. Their findings showed that the epidemic was highly clonal, and network analysis indicated transmission across a network with high levels of interconnectedness. de Celis Pereda et al. tried to estimate the variability in transmission between different multi-drug-resistant *Acinetobacter baumannii* clonal groups using data on carriage on a surgical ward. They identified three clonal complexes by performing molecular fingerprinting, and applied stochastic transmission models to estimate transmission rates for each complex. Results suggested that one of the clones had enhanced transmissibility compared with the other two clones, and further explained local epidemic dynamics. Finally, Kumar et al. optimized cluster identification by organizing multi-drug-resistant Gram-negative bacteria isolates from admitted patients into co-resistance groups, and using schematics of the ward layouts in a Monte Carlo simulation. They concluded that this was ‘a powerful way to quickly identify outbreaks’, and early detection is critical with the decreasing number of effective treatment regimens available.

**Spatiotemporal analysis using GIS**

GIS was used in only 3% (N = 4) of studies identified in this review, demonstrating its limited uptake in the investigation of HCAIs; all of these studies were undertaken in 2000 or later. The studies were conducted hospital-wide, and all but one described a prospective application.

Kistemacker et al. employed GIS for a retrospective investigation of a salmonella outbreak, the source of which could not be identified by biological testing as food samples had been discarded. By mapping the distribution of cases across the hospital site and using analytical tools in GIS, the researchers identified that the sole link between cases was food delivery from a central kitchen. This led to an investigation of food production and the source was discovered.
### Temporal/spatial focus

| First author | Year | Setting | Organism | Molecular methods | Statistical methods | Aim | Study design |
|--------------|------|---------|----------|-------------------|---------------------|-----|-------------|
| T Aldeyab MA | 2009 | Whole hospital | *Clostridium difficile* | N/A | ARIMA time series | Assess impact of AB use | Retrospective |
| T Aldeyab MA | 2008 | Whole hospital | MRSA | N/A | ARIMA time series | Assess impact of AB use | Retrospective |
| T Bertrand X | 2012 | Whole hospital | MRSA | N/A | ARIMA time series | Assess impact of IC measures | Retrospective |
| T Birnbaum D | 1984 | Whole hospital | Multiple | N/A | Outbreak threshold levels | Detect outbreaks | Prospective |
| T Charvat H | 2010 | Whole hospital | Multiple | N/A | Monte Carlo/time interval distance modelling | Detect clusters | Retrospective |
| T Haley RW | 1982 | Paediatric ward | *Staphylococcus aureus* | N/A | Multi-variate statistical model | Assess impact of IC measures | Retrospective |
| T Polgreen PM | 2010 | Multiple hospitals | *Clostridium difficile/influenza* | N/A | Auto-regressive time series analysis | Characterize incidence | Retrospective |
| T Vernaz N | 2008 | Whole hospital | *Clostridium difficile* | N/A | ARIMA time series | Assess impact of AB use | Prospective |
| T and S Kong F | 2012 | Whole hospital | MRSA | N/A | Nested tri-level hierarchical log regression models | Quantify infection risk | Retrospective |
| T and S Kroker P | 2001 | Whole hospital | *Clostridium difficile* | N/A | Knox regression analysis | Detect clusters | Retrospective |
| T and S Rushton SP | 2010 | Intensive care unit | Multiple | N/A | Monte Carlo | Investigate spread of infection | Retrospective |
| T and S Starr JM | 2009 | Whole hospital | *Clostridium difficile* | N/A | Monte Carlo Markov chain analysis | Assess impact of IC measures | Retrospective |
| T and S Yu ITS | 2005 | Whole hospital | SARS | N/A | Cox regression analysis | Outbreak investigation | Retrospective |

### Statistical spatiotemporal analysis with molecular information

| First author | Year | Setting | Organism | Molecular methods | Statistical methods | Aim | Study design |
|--------------|------|---------|----------|-------------------|---------------------|-----|-------------|
| T de Celles MD | 2012 | Surgical ward | MDRAB | repPCR | Stochastic transmission model | Assess impact of molecular typing | Retrospective |
| T Gandhi NR | 2013 | Whole hospital | XDRTB | RFLP | Network analysis | Investigate transmission | Retrospective |
| T Nübel U | 2013 | Paediatric ward | MRSA | SNP analysis | Bayesian skylines | Identify risk factors | Retrospective |
| T and S Kumar VS | 2006 | Whole hospital | MDRGN | Not stated | Monte Carlo/SatScan | Detect clusters | Retrospective |
used GIS to undertake geostatistical analysis of local antibiotic resistance to act as an early warning system for the emergence of drug-resistant strains, enabling doctors to alter their prescription practices. Kho et al. developed and implemented GIS software that enabled them to demonstrate inappropriate patient placement and insufficient hand hygiene in 14% of healthcare provider—patient contacts. Kwan et al. incorporated GIS successfully in a wide range of hospital-based investigations. Using GIS as the central repository for spatial and temporal data of infectious disease cases, the collected data were queried and analysed to identify disease clusters. The results were then communicated to the appropriate personnel, helping decision makers to target control efforts.

**Discussion**

This review highlights numerous \((N = 146)\) studies focusing on spatiotemporal investigations of infectious diseases within healthcare settings; however, very few of these \((N = 22)\) used appropriate statistical methods to confirm transmission or clustering. This suggests that spatiotemporal data are regularly collected in healthcare settings to examine the potential for clustering, but confirmation using statistical analysis is infrequent, which introduces the risk of misinterpretation and hence development of less effective interventions and management of the problem. Of note, most of the published descriptive analyses were also retrospective, and in the absence of further statistical testing, provide little information for future prevention or prediction activities. Similarly, while half of all identified studies included molecular techniques for differentiating clusters, many of these were older techniques used to determine very large differences in bacteria, and are not conclusive. Only 7% of studies that included molecular data also used statistical analyses to provide more quantitative evidence of transmission clusters.

**Underuse of data**

This review found that while the collection of spatiotemporal data has been integral to HCAI prevention activities for decades, the use of spatiotemporal statistical analysis is relatively new to the study of HCAIs in comparison with infectious diseases occurring within the community. Most of the studies identified in this review used spatial and temporal information to provide a qualitative description of disease occurrence by time/space, and in contrast to those that employed more sophisticated analyses, were limited in the scope of their findings. Naturally, the ways in which spatial or temporal data are used within investigations of HCAIs varied greatly, and presentation depended upon the aim of each study. However, the large amount of data collected was often not used to its full potential, and opportunities to gain a more thorough understanding of the problem were missed.

The ability of descriptive studies to identify any significant influences of infectious disease dynamics is limited. Several studies discussed the significance of the geographical distribution of cases without undertaking any analyses, which is a serious issue as sharing the same geographical space does not prove that transmission has occurred. The smaller the scale at which populations are studied, the greater the possibility that ‘clustering’ of cases could have occurred due to a
confounding factor (e.g. cohorting of high-risk patients). This highlights a missed opportunity to learn more about the spread of organisms within healthcare settings, and to develop more effective intervention strategies based upon transmission dynamics within that particular setting.

Maximizing data usage

It is extremely important that hospitals are able to understand the local HCAI epidemiology to inform their routine practice, rather than generalizing evidence from other settings. A major stumbling block can be the perception that these analyses may involve active data collection; however, an abundance of existing datasets could be used. Examples of disparity in data usage are the studies by Kroker et al. and Mody et al., in which they attempted to identify potential clusters of C. difficile within their hospitals. Both studies were published in 2001 and used clinical patient notes and laboratory results for C. difficile toxin assays. Mody et al. defined a cluster arbitrarily as one or more cases occurring within 21 days of a previous case on the same nursing unit, and used this to identify temporal clusters within their dataset; however, they were unable to suggest potential factors related to the observed pattern. Kroker et al. employed the Knox test to identify time-space clusters, which highlighted hospital geography and traffic between wards as significant factors, and enabled them to adapt their infection control procedures.

Incorporation of molecular data into investigations can have a profound impact on the effectiveness of any outbreak response. Recent advances in molecular biology, such as rapid benchtop sequencing, have led to a revolution in the detail that can be gained from clinical samples. While many hospitals only perform basic identification of micro-organisms due to the resources available, this data, when available, can be useful to enhance current investigations. A study by Adams et al. in 1981 investigated nosocomial infections on a paediatric intensive care unit, and was able to distinguish that there had been two separate outbreaks involving separate strains of herpes simplex virus type 1. The initial investigation, which had not included molecular data, concluded that all cases belonged to a single outbreak, and thus limited the impact of their initial control measures.

Benefits of incorporating statistical testing

Molecular data can be invaluable in ruling out a link between cases; however, as emphasized in the study by Helweg-Larsen et al., clusters of infections can occur for many reasons and are often caused by factors other than nosocomial spread. Therefore, incorporation of true temporal or spatial analysis, to eliminate similarity of micro-organisms by chance, alongside molecular techniques could lead to a better understanding of the true transmission dynamics, as inappropriate assumptions are often made about clustering when based solely on molecular data.

Prior to 2000, only two studies were identified that had performed spatial or temporal analysis; in the last decade, this number has increased to 11. This may be due, in part, to the development of novel statistical methods and further advancement of user-friendly statistical and GIS software; however, the majority of the statistical methods in these studies have been widely employed in other fields since before the 1980s. The increased use of electronic databases in hospitals for storage of medical information has created a rich source of epidemiologically and clinically relevant information, allowing more detailed analyses to be performed.

The major aim of this review was to identify how spatio-temporal analyses have been used previously, and to suggest how they can be employed to benefit practices within healthcare settings. The Knox test is a simple analysis that can be used to identify clustering, and methods using outbreak thresholds are common within infection control reporting. However, the ideal situation is to design control programmes based upon the dynamics and processes observed within the local institution.

As randomized controlled trials can be difficult or costly to undertake in clinical settings, some authors have employed predictive modelling techniques to build their own evidence base. For example, Rushton et al. used a statistical approach to investigate clustering and patterns of spread of a number of organisms within an intensive treatment unit. They obtained data from pre-existing datasets including numbers of infected patients, admission details, duration of stay and bed movement, whilst they estimated some additional variables from evaluating nurse–patient contacts. They identified variation in the degree of clustering of different organisms, and tested the impact of potential control interventions in the model. The findings suggest that bed movement and staff–patient contacts have to be controlled, and control strategies may need to be organism-specific.

Recommendations

Spatiotemporal analysis can distil a much greater amount of relevant information from data collected on HCAIs than purely descriptive studies. Analysis is key to furthering understanding of the epidemiology and dynamics of transmission of these organisms. The underuse of spatial and temporal data may be due to the primary focus of studies on retrospective actions in response to an outbreak, and this ‘fire-fighting’ approach may be propagated by institutional goals. However, new sophisticated techniques allow for greater adaptability to the current challenges in health care, including increased cohorting of at-risk patients, spread of resistance and the corresponding decrease in the number of available effective antimicrobials. A focused approach on development of understanding of HCAI epidemiology is likely to lead to identification of significant risk factors and better prevention.

Molecular typing technology is quickly moving from research to clinical settings, and it is becoming more common for detailed molecular analyses to be undertaken to investigate nosocomial infections. From this review, it is clear that the uptake of statistical analyses is the limiting step in moving towards modern sophisticated analyses of HCAIs. Few healthcare workers have the training to develop statistical models or perform in-depth analyses, and this is where collaboration with academic institutions can be exploited to improve the understanding of local disease dynamics without massively increasing the costs to hospitals. These collaborations would provide rich datasets for researchers to use, while enabling clinicians to employ cutting-edge methodologies that will inform their routine practice.

One possible intermediary step would be to further the use of GIS for HCAI investigations, as it enables a wide range of
analyses to be undertaken within one piece of software in which staff could be trained. Whilst the initial implementation may be time and cost intensive, the benefits are clear from the few studies identified in this review. The combination of HCAI datasets from numerous sources in one system and subsequent visualization can enable healthcare workers to incorporate up-to-date infection data into their clinical practice. As hospitals move to combine databases and increase the level of electronic recording, this presents an ideal time to incorporate GIS into these systems and create a fully-integrated hospital information system.

With movement of patients between care structures, differentiation between infection control in primary and secondary care is becoming more important. The small number \((N = 7, 5\%)\) of studies based within nursing homes in this review suggests that less attention has been given to care units outside of hospitals. However, these could act as reservoirs of infections, and regular re-admission of their residents could lead to further hospital transmission. In addition to providing an analytical toolkit for spatial clustering, GIS could improve the understanding of this relationship by enabling healthcare providers to consider the impact of their local community.

The future potential applications in healthcare settings are ever expanding as more sophisticated molecular, statistical and computational techniques become increasingly commonplace. Publication of analytical studies on HCAI in major clinical journals rather than specialized niche journals, as observed in this review, could increase awareness of these techniques and widen their use.

Limitations

In structuring the search strategy for the review, the authors endeavoured to ensure the inclusion of studies from as broad a range as possible. However, due to the great variation in the terminology used across the numerous clinical and scientific fields, it is possible that a few studies were missed. Further, the heterogeneity within the evidence base precluded meta-analysis of the findings. Finally, publication bias cannot be fully avoided in a review.

Conclusion

To truly understand and stem the growing problem of HCAIs worldwide, a multi-disciplinary approach is required. This is dependent on the skills and technology available to those investigating the problem, and is likely to require collaboration between experts. This review suggests that greater integration of spatiotemporal techniques into HCAI investigations could prove invaluable in highlighting previously unobserved patterns of infections, and maximizing the understanding of disease dynamics. Given that infections within a small contained area, such as a hospital, have greater potential for misclassification of clustering, it is necessary to use both molecular techniques and the appropriate spatiotemporal statistical techniques to maximize the accuracy of the study findings. Given the expanding technology of information systems (e.g. electronic medical databases), advancement in molecular and statistical techniques, development of analytical platforms that enable greater access to non-experts and increased interdisciplinary collaboration, the potential for using pre-existing data to prevent future avoidable infections and improve patient safety can become a reality.

Conflict of interest statement
None declared.

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