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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.



## 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%.[1] In addition to causing significant, yet preventable, morbidity and mortality[2] in countries with centrally-funded and managed healthcare systems, such as the UK

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National Health Service, HCAIs increase waiting times and reduce availability of resources to provide care to the population.[3]

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,[4] environment[5]) and increasingly susceptible patients[6] 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.[7]

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.[8]

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,[9] 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.[10] 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,[11] and provide rapid dissemination of information through visualization.[12]

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,[13] 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.[14]

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 HCAIs. 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

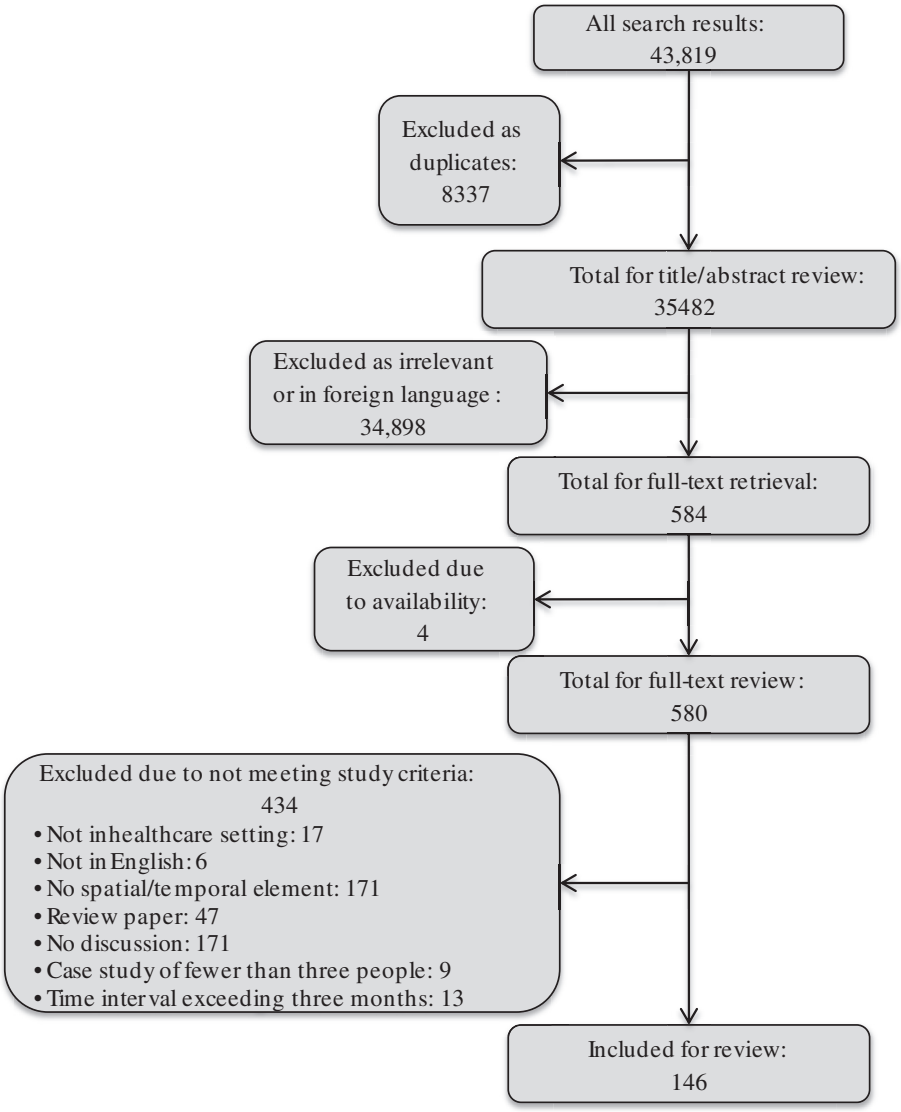


**Figure 1.** Flowchart of article inclusion.

surveillance, whilst the remaining 25% of studies were prospective.

Numerous HCAIs 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 outbreaks[15–22] 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 equipment[30,31] and the physical layout of hospital utilities[32,33]). Only four studies described the spatial distribution of cases to show the impact of hospital renovations[34] or the layout of cases across specialities,[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]

**Table I**
Categories of studies identified in the review

| Study type | Study subtype | Number of papers (%) |
|---|---|---|
| Descriptive ($N = 124$, 85%) | Case reporting | 29 (20) |
| | Basic descriptive epidemiology | 26 (18) |
| | Basic descriptive epidemiology with molecular data | 69 (47) |
| Analytical ($N = 22$, 15%) | Statistical spatiotemporal analysis | 13 (9) |
| | Statistical spatiotemporal analysis with molecular data | 5 (3) |
| | Spatiotemporal analysis using geographic information systems | 4 (3) |

### *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 ward[44] or to display the location of patients.[45–53] 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 clusters[58–62] or provide evidence of potential transmission.[63,64]

A number of studies used timelines to evaluate how cases were linked.[65–67] Chen *et al.* visualized the spread of severe acute respiratory syndrome within an emergency department.[68] 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 dissemination[69–81] or potential sources[82–85] 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,[86–92] 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)[93]; 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 identification[103] and improving control interventions.[104,105] However, the most common applications of

**Table II**
Characteristics of descriptive studies included in the review ($N = 124$)

| Temporal/ spatial focus | First author | Year | Setting | Organism | Molecular methods | Aim | Study design |
|---|---|---|---|---|---|---|---|
| Case reporting | | | | | | | |
| S | Arnow PM | 1978 | Renal ward | *Aspergillus* spp. | N/A | Describe outbreak | Retrospective |
| S | Baird SF | 2011 | Haematology ward | Non-tuberculous mycobacterium | N/A | Outbreak investigation | Retrospective |
| S | Panwalker AP | 1986 | Whole hospital | *Mycobacterium gordonae* | N/A | Describe IC measures | Retrospective |
| S | Patterson JE | 1998 | Geriatric ward | Hib | N/A | Detect clusters | Retrospective |
| T | Addiss DG | 1991 | Nursing home | *Bordetella pertussis* | N/A | Describe outbreak | Retrospective |
| T | Alonso-Echanove J | 2001 | Whole hospital | *Mycobacterium tuberculosis* | N/A | Describe outbreak | Retrospective |
| T | Arnow PM | 1991 | Whole hospital | *Aspergillus* spp. | N/A | Assess environmental contamination | Prospective |
| T | Arnow PM | 1998 | Haematology ward | Bloodstream infection | N/A | Describe outbreak | Retrospective |
| T | Arnow PM | 1982 | Whole hospital | *Legionella pneumophila* | N/A | Describe outbreak | Retrospective |
| T | Bayat A | 2003 | Intensive care unit | Multiple | N/A | Describe outbreak | Retrospective |
| T | Belani A | 1986 | Paediatric ward | *Staphylococcus aureus* | N/A | Describe outbreak | Retrospective |
| T | Bonilla HF | 1997 | Whole hospital | VRE | N/A | Describe incidence | Prospective |
| T | Cartmill TDI | 1994 | Haematology ward | *Clostridium difficile* | N/A | Describe impact of IC measures | Prospective |
| T | Emont SL | 1993 | Nursing home | Gastroenteritis | N/A | Describe incidence | Retrospective |
| T | Fourneret-Vivier A | 2006 | Whole hospital | *Aspergillus* spp. | N/A | Describe incidence | Prospective |
| T | Fowler SL | 1998 | Paediatric ward | *Candida lusitaniae* | N/A | Describe transmission | Retrospective |
| T | Haley CE | 1979 | Whole hospital | *Legionella pneumophila* | N/A | Outbreak investigation | Both |
| T | Klimowski LL | 1989 | Whole hospital | *Aspergillus* spp. | N/A | Describe incidence | Retrospective |
| T | Lai KK | 1998 | Whole hospital | VRE | N/A | Assess impact of IC measures | Prospective |
| T | Larson JL | 2003 | Whole hospital | *Mycobacterium tuberculosis* | N/A | Outbreak investigation | Retrospective |
| T | Ofner-Agostini M | 2006 | Multiple hospitals | SARS | N/A | Review IC policies | Retrospective |
| T | Pegues CF | 2001 | Whole hospital | *Aspergillus* spp. | N/A | Describe incidence | Retrospective |
| T and S | Abulrahi HA | 1997 | Whole hospital | *Plasmodium falciparum* | N/A | Determine transmission route | Prospective |
| T and S | Davies BI | 1999 | Whole hospital | *Streptococcus pyogenes* | N/A | Outbreak investigation | Retrospective |
| T and S | Deutscher M | 2011 | Whole hospital | Group A streptococcus | N/A | Identify risk factors | Retrospective |
| T and S | Helms CM | 1983 | Whole hospital | *Legionella pneumophila* | N/A | Outbreak investigation | Retrospective |
| T and S | MacDonald KS | 1993 | Whole hospital | *Clostridium difficile* | N/A | Describe incidence | Retrospective |
| T and S | McGrathEJ | 2011 | Paediatric ward | *Acinetobacter* spp. | N/A | Determine transmission route | Retrospective |
| T and S | WangH | 2013 | Whole hospital | *Listeria monocytogenes* | N/A | Describe clinical outcomes | Retrospective |
| Basic descriptive epidemiology | | | | | | | |
| S | Lentino JR | 1982 | Whole hospital | *Aspergillus* spp. | N/A | Detect clusters | Retrospective |
| T | Bowen KE | 1995 | Whole hospital | *Clostridium difficile* | N/A | Describe incidence | Retrospective |

(*continued on next page*)

**Table II** (*continued*)

| 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 and S | Alam NK | 2005 | Whole hospital | *Salmonella enterica* | N/A | Describe cluster | Retrospective |
| T and S | Auerbach SB | 1992 | Nursing home | Group A streptococcus | N/A | Outbreak investigation | Retrospective |
| T and S | Barrett SP | 1988 | Whole hospital | MRSA | N/A | Describe incidence | Retrospective |
| T and S | Bitar CM | 1987 | Whole hospital | MRSA | N/A | Describe outbreak | Retrospective |
| T and S | Chen YC | 2004 | A&E | SARS | N/A | Outbreak investigation | Retrospective |
| T and S | Faustini A | 2004 | Whole hospital | Necrotizing enterocolitis | N/A | Outbreak investigation | Retrospective |
| T and S | Foulke GE | 1989 | Intensive care unit | *Clostridium difficile* | N/A | Describe use of IC measures | Retrospective |
| T and S | Goldmann DA | 1981 | Paediatric ward | Multiple | N/A | Describe outbreak | Prospective |
| T and S | Lai KK | 2001 | Transplant ward | *Aspergillus* spp. | N/A | Detect clusters | Retrospective |
| T and S | Mody LR | 2001 | Whole hospital | *Clostridium difficile* | N/A | Describe incidence | Prospective |
| T and S | Pavlov I | 2009 | Whole hospital | *Clostridium difficile* | N/A | Detect clusters | Retrospective |
| T and S | Pegues DA | 1993 | Nursing home | Gastroenteritis | N/A | Outbreak investigation | Retrospective |
| T and S | Strabelli TMV | 2006 | Paediatric ward | *Enterococcus faecalis* | N/A | Detect clusters | Retrospective |
| T and S | Turcios-Ruiz RM | 2008 | Paediatric ward | Norovirus | N/A | Outbreak investigation | Retrospective |
| T and S | 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 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| T | Alfieri N | 1999 | Intensive care unit | *Stenotrophomonas maltophilia* | RFLP | Outbreak investigation | Both |
| T | Allander T | 1995 | Haematology ward | Hepatitis C virus | PCR/NASeq | Detect clusters | Retrospective |
| T | Assadian O | 2002 | Paediatric ward | *Serratia marcescens* | PCR | Describe outbreak | Retrospective |
| T | Aumeran C | 2008 | Whole hospital | VRE | PFGE | Describe use of IC measures | Prospective |
| T | Baddour LM | 1999 | Whole hospital | *Enterococcus faecium* | CHEF | Describe outbreak | Retrospective |
| T | Belmares J | 2009 | Whole hospital | *Clostridium difficile* | REA | Describe incidence | Retrospective |
| T | Ben Abdeljelil J | 2011 | Paediatric ward | *Candida albicans* | PFGE | Investigate strain distribution | Retrospective |
| T | Ben Abdeljelil J | 2012 | Paediatric ward | *Candida albicans* | PFGE | Outbreak investigation | Retrospective |
| T | Brillowska-Dabrowska A | 2009 | Haematology ward | *Candida parapsilosis* | RAPD | Assess impact of molecular typing | Retrospective |
| T | DavinRegli A | 1996 | Intensive care unit | *Enterobacter aerogenes* | RAPD | Outbreak investigation | Prospective |
| T | Eyre DW | 2012 | Multiple hospitals | *Clostridium difficile*/MRSA | SNV analysis | Outbreak investigation | Retrospective |
| T | Falk PS | 2000 | Burns ward | VRE | PFGE | Outbreak investigation | Retrospective |
| T | Geis S | 2013 | Haematology ward | Respiratory syncytial virus | RT-PCR | Outbreak investigation | Retrospective |
| T | Gray J | 2012 | Paediatric ward | *Klebsiella pneumoniae* | PFGE | Detect clusters | Retrospective |
| T | Harvala H | 2012 | Haematology ward | Parainfluenza type 3 | RT-PCR | Outbreak investigation | Retrospective |
| T | Helali NE | 2005 | Whole hospital | *Staphylococcus aureus* | PFGE | Outbreak investigation | Both |
| T | Helweg-Larsen J | 1998 | Whole hospital | *Pneumocystis carinii* | PCR | Detect clusters | Retrospective |
| T | Hong KB | 2012 | Paediatric ward | *Acinetobacter baumannii* | MLST | Outbreak investigation | Retrospective |
| T | Kakis A | 2002 | Whole hospital | Group A streptococcus | M typing/T agglutination | Outbreak investigation | Retrospective |
| T | Layton MC | 1993 | Dermatology ward | MRSA | PFGE | Detect clusters | Retrospective |
| T | L'Ecuyer PB | 1996 | Multiple hospitals | *Salmonella senftenberg* | PFGE | Outbreak investigation | Retrospective |
| T | Le Gal S | 2012 | Renal ward | *Pneumocystis* spp. | RFLP | Detect clusters | Retrospective |
| T | Loudon KW | 1994 | Haematology ward | *Aspergillus fumigatus* | RAPD | Detect clusters | Retrospective |
| T | McAdams RM | 2008 | Paediatric ward | MRSA | PFGE | Detect clusters | Retrospective |
| T | McFarland LV | 1989 | Whole hospital | *Clostridium difficile* | Immunoblot | Describe incidence | Prospective |
| T | Peta M | 2006 | Intensive care unit | *Enterococcus faecium* | PFGE | Outbreak investigation | Both |
| T | Rupp ME | 2001 | Paediatric ward | VRE | PFGE | Outbreak investigation | Prospective |
| T | Sardan YC | 2004 | Whole hospital | *Klebsiella oxytoca* | AP-PCR | Outbreak investigation | Retrospective |
| T | Zoltanski J | 2011 | Paediatric ward | ARGNB | PFGE | Describe incidence | Prospective |
| T and S | Abb J | 2004 | Whole hospital | MRSA | PFGE | Investigate strain distribution | Prospective |
| T and S | Abbo A | 2005 | Whole hospital | *Acinetobacter baumannii* | PFGE | Describe incidence | Retrospective |
| T and S | Arnold KE | 2006 | Nursing home | Group A streptococcus | RFLP | Outbreak investigation | Retrospective |
| T and S | Boyce JM | 1993 | Whole hospital | MRSA | Plasmid typing | Assess impact of IC measures | Retrospective |
| T and S | Byers KE | 2001 | Whole hospital | VRE | PFGE | Assess impact of IC measures | Prospective |
| T and S | Carneiro MAS | 2007 | Haematology ward | Hepatitis C virus | RT-PCR | Investigate strain distribution | Prospective |
| T and S | Chen LF | 2011 | Haematology ward | Influenza A (H1N1) | RT-PCR | Outbreak investigation | Retrospective |

(*continued on next page*)

**Table II** (*continued*)

| 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 | Prospective |
| T and S | Dijkshoorn 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 cenocepacia* | 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 | MRSA | 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[106–114] and whether transmission had occurred.[77,115–121] Many studies evaluated the distribution of strains over time or space,[122–126] 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.[127–133] 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,[134] 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 (Table III). 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[135–137] and *C. difficile*,[138] or if control measures for multiple organisms reduced the incidence.[139] 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,[140,141] 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.[142]

Spatiotemporal studies ($N = 5$) typically aimed to model infections retrospectively to investigate outbreaks and to detect clustering.[8,143] 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 (Table III), 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.[144] 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[145] 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[146] 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 Celles *et al*. tried to estimate the variability in transmission between different multi-drug-resistant *Acinetobacter baumannii* clonal groups[147] 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*.[148] 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 (Table III); all of these studies were undertaken in 2000 or later. The studies were conducted hospital-wide, and all but one described a prospective application.

Kistemann *et al*. employed GIS for a retrospective investigation of a salmonella outbreak,[149] 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. Kruger and Steffen

**Table III**
Characteristics of analytical studies included in the review ($N = 22$)

| Temporal/ spatial focus | First author | Year | Setting | Organism | Molecular methods | Statistical methods | Aim | Study design |
|---|---|---|---|---|---|---|---|---|
| Statistical spatiotemporal analysis | | | | | | | | |
| 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 | 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 | | | | | | | | |
| 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 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| T and S | Rexach, CE | 2005 | Whole hospital | *Clostridium difficile* | AP-PCR | Knox regression analysis | Investigate transmission | Retrospective |
| Spatiotemporal analysis using GIS | | | | | | | | |
| S | Kistemann, T | 2000 | Whole hospital | *Salmonella enteritidis* | N/A | Geographical distribution | Outbreak investigation | Retrospective |
| S | Kruger, H | 2002 | Multiple hospitals | Multiple | N/A | Mapping of resistant isolates | Mapping distribution | Prospective |
| T and S | Kho, A | 2006 | Whole hospital | MRSA/VRE | N/A | Visualization of HCW movement | Identify risk factors | Prospective |
| T and S | Kwan, MYW | 2009 | Whole hospital | Multiple | N/A | IC | Investigate spread of infection | Prospective |

T, temporal; S, spatial; N/A, not applicable; MRSA, meticillin-resistant *Staphylococcus aureus*; BSI, bloodstream infection; SARS, severe acute respiratory syndrome; MDRAB, multi-drug-resistant *Acinetobacter baumannii*; XDRTB, extensively-drug-resistant tuberculosis; SNP, single nucleotide polymorphism; MDRGN, multi-drug-resistant Gram-negative bacteria; VRE, vancomycin-resistant enterococci; repPCR, repetitive element palindromic polymerase chain reaction; AP-PCR, arbitrarily primed polymerase chain reaction; RFLP, restriction fragment length polymorphism; AB, antibiotic; HCW, healthcare worker; IC, infection control.

used GIS to undertake geostatistical analysis of local antibiotic resistance to act as an early warning system for the emergence of drug-resistant strains,[150] 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.[151] Kwan *et al.* incorporated GIS successfully in a wide range of hospital-based investigations.[12] 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.[9] 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,[48,64,68] which is a serious issue as sharing the same geographical space does not prove that transmission has occurred.[19,133] 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.[83]

### 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.[8,62] 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.[88] 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.[76] 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.[7] 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 spatiotemporal 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.[143] 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,[149] 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 difficult. 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.

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None declared.

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## References

1. World Health Organization. *Report on the burden of endemic health care-associated infection worldwide*. Geneva: World Health Organization; 2011.
2. Zingg W, Sax H, Inan C, *et al*. Hospital-wide surveillance of catheter-related bloodstream infection: from the expected to the unexpected. *J Hosp Infect* 2009;**73**:41–46.
3. Millar M. Patient rights and healthcare-associated infection. *J Hosp Infect* 2011;**79**:99–102.
4. Sanderson PJ, Weissler S. Recovery of coliforms from the hands of nurses and patients: activities leading to contamination. *J Hosp Infect* 1992;**21**:85–93.
5. Arnow PM, Sadigh M, Costas C, Weil D, Chudy R. Endemic and epidemic aspergillosis associated with in-hospital replication of aspergillus organisms. *J Infect Dis* 1991;**164**:998–1002.
6. Maki DG. Nosocomial bacteremia. An epidemiologic overview. *Am J Med* 1981;**70**:719–732.
7. Helweg-Larsen J, Tsolaki A, Miller R, Lundgren B, Wakefield A. Clusters of *Pneumocystis carinii* pneumonia: analysis of person-to-person transmission by genotyping. *Q J Med* 1998;**91**:813–820.
8. Kroker P, Bower M, Azadian B. *Clostridium difficile* infection, hospital geography and time–space clustering. *Q J Med* 2001;**94**:223–225.
9. Sarkar R, Prabhakar AT, Manickam S, *et al*. Epidemiological investigation of an outbreak of acute diarrhoeal disease using geographic information systems. *Trans R Soc Trop Med Hyg* 2007;**101**:587–593.
10. Guajardo OA, Oyana TJ. A critical assessment of geographic clusters of breast and lung cancer incidences among residents living near the Tittabawassee and Saginaw Rivers, Michigan, USA. *J Environ Public Health* 2009;**2009**:316249.
11. Graham AJ, Atkinson PM, Danson FM. Spatial analysis for epidemiology. *Acta Trop* 2004;**91**:219–225.
12. Kwan MYW, Cheung WK, Tsang TY, Tsang KY, Tong WK, Chow CB. Use of geographical information system in infectious diseases surveillance in hospital. *H K J Paediatr* 2009;**14**:298–299.
13. Garcia AL, Aylin P, Tian J, *et al*. Data linkage between existing healthcare databases to support hospital epidemiology. *J Hosp Infect* 2011;**79**:231–235.
14. Yu ITS, Wong TW, Chiu YL, Lee N, Li YG. Temporal-spatial analysis of severe acute respiratory syndrome among hospital in-patients. *Clin Infect Dis* 2005;**40**:1237–1243.
15. Helms CM, Massanari RM, Zeitler R, *et al*. Legionnaires disease associated with a hospital water-system – a cluster of 24 nosocomial cases. *Ann Intern Med* 1983;**99**:172–178.
16. Baird SF, Taori SK, Dave J, Willocks LJ, Roddie H, Hanson M. Cluster of non-tuberculous mycobacteraemia associated with

water supply in a haemato-oncology unit. *J Hosp Infect* 2011;**79**:339—343.
17. Davies BI, Hirsch J, Werink TJ, Toenbreker H, Bainczijk F, van Leeuwen WJ. A *Streptococcus pyogenes* outbreak caused by an unusual serotype of low virulence: the value of typing techniques in outbreak investigations. *J Infect* 1999;**38**:185—190.
18. McGrath E, Chopra T, AbdeHaq N, *et al*. An outbreak of carbapenem-resistant *Acinetobacter baumannii* infection in a neonatal intensive care unit: investigation and control. *Infect Control Hosp Epidemiol* 2011;**32**:34—41.
19. Emont SL, Cote TR, Dwyer DM, Horan JM. Gastroenteritis outbreak in a Maryland nursing home. *Md Med J* 1993;**42**:1099—1103.
20. Addiss DG, Davis JP, Meade BD, *et al*. A pertussis outbreak in a Wisconsin USA nursing home. *J Infect Dis* 1991;**164**:704—710.
21. Alonso-Echanove J, Granich RM, Laszlo A, *et al*. Occupational transmission of *Mycobacterium tuberculosis* to health care workers in a university hospital in Lima, Peru. *Clin Infect Dis* 2001;**33**:589—596.
22. Wang HL, Ghanem KG, Wang P, Yang S, Li TS. Listeriosis at a tertiary care hospital in Beijing, China: high prevalence of non-clustered healthcare-associated cases among adult patients. *Clin Infect Dis* 2013;**56**:666—676.
23. Lai KK, Kelley AL, Melvin ZS, Belliveau PP, Fontecchio SA. Failure to eradicate vancomycin-resistant enterococci in a university hospital and the cost of barrier precautions. *Infect Control Hosp Epidemiol* 1998;**19**:647—652.
24. Cartmill TDI. Management and control of a large outbreak of diarrhoea due to *Clostridium difficile*. *J Hosp Infect* 1994;**27**:1—15.
25. Deutscher M, Schillie S, Gould C, *et al*. Investigation of a group A streptococcal outbreak among residents of a long-term acute care hospital. *Clin Infect Dis* 2011;**52**:988—994.
26. Belani A, Sherertz RJ, Sullivan ML, Russell BA, Reumen PD. Outbreak of staphylococcal infection in two hospital nurseries traced to a single nasal carrier. *Infect Control* 1986;**7**:487—490.
27. Patterson JE, Madden GM, Krisiunas EP, *et al*. A Nosocomial outbreak of ampicillin-resistant *Haemophilus influenzae* type b in a geriatric unit. *J Infect Dis* 1988;**157**:1002—1007.
28. Ofner-Agostini M, Gravel D, McDonald LC, *et al*. Cluster of cases of severe acute respiratory syndrome among Toronto healthcare workers after implementation of infection control precautions: a case series. *Infect Control Hosp Epidemiol* 2006;**27**:473—478.
29. Fowler SL, Rhoton B, Springer SC, Messer SA, Hollis RJ, Pfaller MA. Evidence for person-to-person transmission of *Candida lusitaniae* in a neonatal intensive-care unit. *Infect Control Hosp Epidemiol* 1998;**19**:343—345.
30. Arnow PM, Garcia-Houchins S, Neagle MB, Bova JL, Dillon JJ, Chou T. An outbreak of bloodstream infections arising from hemodialysis equipment. *J Infect Dis* 1998;**178**:783—791.
31. Abulrahi HA, Bohlega EA, Fontaine RE, Al-Seghayer SM, Al-Ruwais AA. *Plasmodium falciparum* malaria transmitted in hospital through heparin locks. *Lancet* 1997;**349**:23—25.
32. Bayat A, Shaaban H, Dodgson A, Dunn KW. Implications for burns unit design following outbreak of multi-resistant acinetobacter infection in ICU and burns unit. *Burns* 2003;**29**:303—306.
33. Larson JL, Lambert L, Stricof RL, Driscoll J, McGarry MA, Ridzon RE. Potential nosocomial exposure to *Mycobacterium tuberculosis* from a bronchoscope. *Infect Control Hosp Epidemiol* 2003;**24**:825—830.
34. Panwalker AP, Fuhse E. Nosocomial *Mycobacterium gordonae* pseudoinfection from contaminated ice machines. *Infect Control* 1986;**7**:67—70.
35. Arnow PM, Andersen RL, Mainous PD, Smith EJ. Pulmonary aspergillosis during hospital renovation. *Am Rev Respir Dis* 1978;**118**:49—54.
36. MacDonald KS, McLeod J, Nicolle L. *Clostridium difficile* enteritis in a Canadian tertiary care hospital. *Can J Infect Control* 1993;**8**:37—40.
37. Klimowski LL, Rotstein C, Cummings KM. Incidence of nosocomial aspergillosis in patients with leukemia over a twenty-year period. *Infect Control Hosp Epidemiol* 1989;**10**:299—305.
38. Pegues CF, Daar ES, Murthy AR. The epidemiology of invasive pulmonary aspergillosis at a large teaching hospital. *Infect Control Hosp Epidemiol* 2001;**22**:370—374.
39. Haley CE, Cohen ML, Halter J, Meyer RD. Nosocomial legionnaires' disease: a continuing common-source epidemic at Wadsworth Medical Center. *Ann Intern Med* 1979;**90**:583—586.
40. Arnow PM, Chou T, Weil D, Shapiro EN, Kretzschmar C. Nosocomial legionnaires' disease caused by aerosolized tap water from respiratory devices. *J Infect Dis* 1982;**146**:460—467.
41. Bonilla HF, Zervos MA, Lyons MJ, *et al*. Colonization with vancomycin-resistant *Enterococcus faecium*: comparison of a long-term-care unit with an acute-care hospital. *Infect Control Hosp Epidemiol* 1997;**18**:333—339.
42. Fourneret-Vivier A, Lebeau B, Mallaret M, *et al*. Hospital-wide prospective mandatory surveillance of invasive aspergillosis in a French teaching hospital (2000—2002). *J Hosp Infect* 2006;**62**:22—28.
43. Lentino JR, Rosenkranz MA, Michaels JA, Kurup VP, Rose HD, Rytel MW. Nosocomial aspergillosis — a retrospective review of airborne disease secondary to road construction and contaminated air conditioners. *Am J Epidemiol* 1982;**116**:430—437.
44. Gomersall CD, Joynt GM, Ho OM, *et al*. Transmission of SARS to healthcare workers. The experience of a Hong Kong ICU. *Intens Care Med* 2006;**32**:564—569.
45. Auerbach SB, Schwartz B, Williams D, *et al*. Outbreak of invasive group A streptococcal infections in a nursing home — lessons on prevention and control. *Arch Intern Med* 1992;**152**:1017—1022.
46. Strabelli TMV, Cais DP, Zeigler R, *et al*. Clustering of *Enterococcus faecalis* infections in a cardiology hospital neonatal intensive care unit. *Braz J Infect Dis* 2006;**10**:113—116.
47. Foulke GE, Silva J. *Clostridium difficile* in the intensive care unit: management problems and prevention issues. *Crit Care Med* 1989;**17**:822—826.
48. Barrett SP, Gill ON, Mellor JA, Bryant JC. A descriptive survey of uncontrolled methicillin-resistant *Staphylococcus aureus* in a twin site general hospital. *Postgrad Med J* 1988;**64**:606—609.
49. Pegues DA, Woernle CH. An outbreak of acute nonbacterial gastroenteritis in a nursing home. *Infect Control Hosp Epidemiol* 1993;**14**:87—94.
50. Faustini A, Forastiere F, Rossi P, Perucci C. An epidemic of gastroenteritis and mild necrotizing enterocolitis in two neonatal units of a university hospital in Rome, Italy. *Epidemiol Infect* 2004;**132**:455—465.
51. Lai KK. A cluster of invasive aspergillosis in a bone marrow transplant unit related to construction and the utility of air sampling. *Am J Infect Control* 2001;**29**:333—337.
52. Gastmeier P, Groneberg K, Weist K, Rueden H. A cluster of nosocomial *Klebsiella pneumoniae* bloodstream infections in a neonatal intensive care department: identification of transmission and intervention. *Am J Infect Control* 2003;**31**:424—430.
53. Warren D, Nelson KE, Farrar JA, *et al*. A large outbreak of epidemic keratoconjunctivitis: problems in controlling nosocomial spread. *J Infect Dis* 1989;**160**:938—943.
54. Goldmann DA, William AD, Freeman J. Nosocomial infections in a neonatal intensive care unit. *J Infect Dis* 1981;**144**:449—459.
55. Burwen DR, Lasker BA, Rao N, Durry E, Padhye AA, Jarvis WR. Invasive aspergillosis outbreak on a hematology-oncology ward. *Infect Control Hosp Epidemiol* 2001;**22**:45—48.
56. Bitar CM, Mayhall CG, Lamb VA, Bradshaw TJ, Spadora AC, Dalton HP. Outbreak due to methicillin- and rifampin-resistant *Staphylococcus aureus*: epidemiology and eradication of the resistant strain from the hospital. *Infect Control* 1987;**8**:15—23.
57. Degail MA, Hughes GJ, Maule C, *et al*. A human metapneumovirus outbreak at a community hospital in England, July to September 2010. *Euro Surveill* 2012;**17**:pii=20145.

58. Kimura AC, Calvet H, Higa JI, *et al*. Outbreak of *Ralstonia pickettii* bacteremia in a neonatal intensive care unit. *Pediatr Infect Dis J* 2005;**24**:1099–1103.
59. Pavlov I, Weiss K, Dubreuil M. The importance of temporal and spatial clusters of *Clostridium difficile* infections (CDI) in a teaching hospital over a 2-year period. *Int J Antimicrob Agents* 2009;**34**(Suppl. 4):S73.
60. Fretz R, Schmid D, Jelovcan S, *et al*. An outbreak of norovirus gastroenteritis in an Austrian hospital, winter 2006–2007. *Wien Klin Wochenschr* 2009;**121**:137–143.
61. Turcios-Ruiz RM, Axelrod P, John KS, *et al*. Outbreak of necrotizing enterocolitis caused by norovirus in a neonatal intensive care unit. *J Pediatr* 2008;**153**:339–344.
62. Mody LR, Smith SM, Dever LL. *Clostridium difficile*-associated diarrhea in a VA medical center: clustering of cases, association with antibiotic usage, and impact on HIV-infected patients. *Infect Control Hosp Epidemiol* 2001;**22**:42–45.
63. Buchbinder N, Dumesnil C, Pinquier D, *et al*. Pandemic A/H1N1/2009 influenza in a paediatric haematology and oncology unit: successful management of a sudden outbreak. *J Hosp Infect* 2011;**79**:155–160.
64. Alam NK, Armstrong PK, Nguyen OT, Kesson AM, Cripps TM, Corbett SJ. *Salmonella typhimurium* phage type 170 in a tertiary paediatric hospital with person-to-person transmission implicated. *Commun Dis Intell* 2005;**29**:374–378.
65. Burney MI, Ghafoor A, Saleen M. Nosocomial outbreak of viral hemorrhagic fever caused by Crimean hemorrhagic fever–Congo virus in Pakistan, January 1976. *Am J Trop Med Hyg* 1980;**29**(5):941–947.
66. Bowen KE, McFarland LV, Greenberg RN, Ramsey MM, Record KE, Svenson J. Isolation of *Clostridium difficile* at a university hospital: a two-year study. *Clin Infect Dis* 1995;**20**:S261–S262.
67. Kaplan JE, Schonberger LB, Varano G, Jackman N, Bied J, Gary GW. An outbreak of acute nonbacterial gastroenteritis in a nursing home demonstration of person-to-person transmission by temporal clustering of cases. *Am J Epidemiol* 1982;**116**:940–948.
68. Chen YC, Huang LM, Chan C, *et al*. SARS in hospital emergency room. *Emerg Infect Dis* 2004;**10**:782–788.
69. Culebras E, González-Romo F, Head J, Gómez M, Morales G, Picazo JJ. Outbreak of *Acinetobacter baumannii* producing OXA-66 in a Spanish hospital: epidemiology and study of patient movements. *Microb Drug Resist* 2010;**16**:309–315.
70. Levidiotou S, Galanakis E, Vrioni G, Papamichael D, Nakos G, Stefanou D. A multi-resistant *Acinetobacter baumannii* outbreak in a general intensive care unit. *In Vivo* 2002;**16**:117–122.
71. Graindorge A, Menard A, Neto M, *et al*. Epidemiology and molecular characterization of a clone of *Burkholderia cenocepacia* responsible for nosocomial pulmonary tract infections in a French intensive care unit. *Diagn Microbiol Infect Dis* 2010;**66**:29–40.
72. Ben Abdeljelil J, Saghrouni F, Emira N, *et al*. Molecular typing of *Candida albicans* isolates from patients and health care workers in a neonatal intensive care unit. *J Appl Microbiol* 2011;**111**:1235–1249.
73. Gray J, Arvelo W, McCracken J, *et al*. An outbreak of *Klebsiella pneumoniae* late-onset sepsis in a neonatal intensive care unit in Guatemala. *Am J Infect Control* 2012;**40**:516–520.
74. Le Gal S, Damiani C, Rouille A, *et al*. A cluster of pneumocystis infections among renal transplant recipients: molecular evidence of colonized patients as potential infectious sources of *Pneumocystis jirovecii*. *Clin Infect Dis* 2012;**54**:E62–E71.
75. Diab-Elschahawi M, Forstner C, Hagen F, *et al*. Microsatellite genotyping clarified conspicuous accumulation of *Candida parapsilosis* at a cardiothoracic surgery intensive care unit. *J Clin Microbiol* 2012;**50**:3422–3426.
76. Adams G, Stover BH, Keenlyside RA, *et al*. Nosocomial herpetic infections in a pediatric intensive care unit. *Am J Epidemiol* 1981;**113**:126–132.
77. Ben AJ, Saghrouni F, Khammari I, *et al*. Investigation of a cluster of *Candida albicans* invasive candidiasis in a neonatal intensive care unit by pulsed-field gel electrophoresis. *Sci World J* 2012;**2012**:138989.
78. Abdallah IM, Araj GF, Matar GM, Abdelnour G, Uwaydah M, Abdelnoor AM. Polymerase chain reaction identification of coagulase-negative staphylococci and of strain diversity and spread of *Staphylococcus epidermidis* in a major medical center in Lebanon. *Infect Control Hosp Epidemiol* 2006;**27**:781–783.
79. Dijkshoorn L, Van Dalen R, Van Ooyen A, *et al*. Endemic acinetobacter in intensive care units: epidemiology and clinical impact. *J Clin Pathol (Lond)* 1993;**46**:533–536.
80. Traub WH, Scheidhauer R, Leonard B, Bauer D. Surveillance of *Pseudomonas aeruginosa* in intensive care units: clusters of nosocomial cross-infection and encounter of a multiple-antibiotic resistant strain. *Chemotherapy* 1998;**44**:243–259.
81. Widmer AF, Wenzel RP, Trilla A, Bale MJ, Jones RN, Doebbeling BN. Outbreak of *Pseudomonas aeruginosa* infections in a surgical intensive-care unit – probable transmission via hands of a health-care worker. *Clin Infect Dis* 1993;**16**:372–376.
82. Carneiro MAS, Teles SA, Lampe E, *et al*. Molecular and epidemiological study on nosocomial transmission of HCV in hemodialysis patients in Brazil. *J Med Virol* 2007;**79**:1325–1333.
83. DavinRegli A, Saux F, Bollet C, Gouin F, DeMicco F. Investigation of outbreaks of *Enterobacter aerogenes* colonisation and infection in intensive care units by random amplification of polymorphic DNA. *J Med Microbiol* 1996;**44**:89–98.
84. Cuny C, Schassan HH, Witte W. Outbreak of nosocomial infections with two different MRSA strains involved: significance of genomic DNA fragment patterns in strains otherwise difficult to type. *Epidemiol Infect* 1993;**111**:55–61.
85. Chen LF, Dailey NJM, Rao AK, *et al*. Cluster of oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infections on a hospital ward among immunocompromised patients – North Carolina, 2009. *J Infect Dis* 2011;**203**:838–846.
86. Assadian O, Berger A, Aspöck C, Mustafa S, Kohlhauser C, Hirschl AM. Nosocomial outbreak of *Serratia marcescens* in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2002;**23**:457–461.
87. Allander T, Gruber A, Nagöhavi M, *et al*. Frequent patient-to-patient transmission of hepatitis C virus in a haematology ward. *Lancet (N Am Edn)* 1995;**345**:603–607.
88. Eyre DW, Golubchik T, Gordon NC, *et al*. A pilot study of rapid benchtop sequencing of *Staphylococcus aureus* and *Clostridium difficile* for outbreak detection and surveillance. *BMJ Open* 2012;**2**:e001124.
89. Englund JA, Anderson LJ, Rhame FS. Nosocomial transmission of respiratory syncytial virus in immunocompromised adults. *J Clin Microbiol* 1991;**29**:115–119.
90. Geis S, Prifert C, Weissbrich B, *et al*. Molecular characterization of a respiratory syncytial virus outbreak in a hematology unit in Heidelberg, Germany. *J Clin Microbiol* 2013;**51**:155–162.
91. Lutz BD, Jin J, Rinaldi MG, Wickes BL, Huycke MM. Outbreak of invasive aspergillus infection in surgical patients, associated with a contaminated air-handling system. *Clin Infect Dis* 2003;**37**:786–793.
92. Belmares J, Johnson S, Parada JP, *et al*. Molecular epidemiology of *Clostridium difficile* over the course of 10 years in a tertiary care hospital. *Clin Infect Dis* 2009;**49**:1141–1147.
93. Alfieri N, Ramotar K, Armstrong P, *et al*. Two consecutive outbreaks of *Stenotrophomonas maltophilia* (*Xanthomonas maltophilia*) in an intensive-care unit defined by restriction fragment-length polymorphism typing. *Infect Control Hosp Epidemiol* 1999;**20**:553–556.
94. Falk PS, Winnike J, Woodmansee C, Desai M, Mayhall CG. Outbreak of vancomycin-resistant enterococci in a burn unit. *Infect Control Hosp Epidemiol* 2000;**21**:575–582.

95. Rupp ME, Marion N, Fey PD, *et al*. Outbreak of vancomycin-resistant *Enterococcus faecium* in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2001;**22**:301–303.
96. McAdams RM, Ellis MW, Trevino S, Rajnik M. Spread of methicillin-resistant *Staphylococcus aureus* USA300 in a neonatal intensive care unit. *Pediatr Int* 2008;**50**:810–815.
97. Peta M, Carretto E, Barbarini D, *et al*. Outbreak of vancomycin-resistant *Enterococcus* spp. in an Italian general intensive care unit. *Clin Microbiol Infect* 2006;**12**:163–169.
98. Layton MC, Perez M, Heald P, Patterson JE. An outbreak of mupirocin-resistant *Staphylococcus aureus* on a dermatology ward associated with an environmental reservoir. *Infect Control Hosp Epidemiol* 1993;**14**:369–375.
99. L'Ecuyer PB, Diego J, Murphy D, *et al*. Nosocomial outbreak of gastroenteritis due to *Salmonella senftenberg*. *Clin Infect Dis* 1996;**23**:734–742.
100. Debast SB, Meis JF, Melchers WJ, Hoogkamp-Korstanje JA, Voss A. Use of interrepeat PCR fingerprinting to investigate an *Acinetobacter baumannii* outbreak in an intensive care unit. *Scand J Infect Dis* 1996;**28**:577–581.
101. Harvala H, Gaunt E, McIntyre C, *et al*. Epidemiology and clinical characteristics of parainfluenza virus 3 outbreak in a haemato-oncology unit. *J Infect* 2012;**65**:246–254.
102. Zoltanski J, Dul M, O'Riordan MA, Blumer J, Toltzis P. Low frequency of endemic patient-to-patient transmission of antibiotic-resistant Gram-negative bacilli in a pediatric intensive care unit. *Infect Control Hosp Epidemiol* 2011;**32**:915–917.
103. Hoefnagels-Schuerman A, Borremans A, Peetermans W, Van Lierde S, Reybrouck G, Van Eldere J. Origin and transmission of methicillin-resistant *Staphylococcus aureus* in an endemic situation: differences between geriatric and intensive-care patients. *J Hosp Infect* 1997;**36**:209–222.
104. Adachi JA, Perego C, Graviss L, *et al*. The role of interventional molecular epidemiology in controlling clonal clusters of multidrug resistant *Pseudomonas aeruginosa* in critically ill cancer patients. *Am J Infect Control* 2009;**37**:442–446.
105. Kondili LA, Genovese D, Argentini C, *et al*. Nosocomial transmission in simultaneous outbreaks of hepatitis C and B virus infections in a hemodialysis center. *Eur J Clin Microbiol Infect Dis* 2006;**25**:527–531.
106. Hong KB, Oh HS, Song JS, *et al*. Investigation and control of an outbreak of imipenem-resistant *Acinetobacter baumannii* infection in a pediatric intensive care unit. *Pediatr Infect Dis J* 2012;**31**:685–690.
107. Mcfarland LV, Mulligan ME, Kwok RYY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. *N Engl J Med* 1989;**320**:204–210.
108. Sardan YC, Zarakolu P, Altun B, *et al*. A cluster of nosocomial *Klebsiella oxytoca* bloodstream infections in a university hospital. *Infect Control Hosp Epidemiol* 2004;**25**:878–882.
109. Helali N, Carbonne A, Naas T, *et al*. Nosocomial outbreak of staphylococcal scalded skin syndrome in neonates: epidemiological investigation and control. *J Hosp Infect* 2005;**61**:130–138.
110. Ferroni A, Nguyen L, Pron B, Quesne G, Brusset M, Berche P. Outbreak of nosocomial urinary tract infections due to *Pseudomonas aeruginosa* in a paediatric surgical unit associated with tap-water contamination. *J Hosp Infect* 1998;**39**:301–307.
111. Loudon KW, Coke AP, Burnie JP, Lucas GS, Yin JAL. Invasive aspergillosis – clusters and sources. *J Med Vet Mycol* 1994;**32**:217–224.
112. Venezia RA, Agresta MD, Hanley EM, Urquhart K, Schoonmaker D. Nosocomial legionellosis associated with aspiration of nasogastric feedings diluted in tap water. *Infect Control Hosp Epidemiol* 1994;**15**:529–533.
113. Baddour LM, Harris E, Huycke MM, Smith AE, Himelright IM. Outbreak of pseudobacteremia due to multidrug-susceptible *Enterococcus faecium*. *Clin Infect Dis* 1999;**28**:1333–1334.
114. Abb J. Frequency and diversity of molecular epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates from patients of a South West German teaching hospital. *J Hosp Infect* 2004;**56**:232–235.
115. Brillowska-Dabrowska A, Schon T, Pannanusorn S, *et al*. A nosocomial outbreak of *Candida parapsilosis* in southern Sweden verified by genotyping. *Scand J Infect Dis* 2009;**41**:135–142.
116. Aita J, Barrera L, Reniero A, *et al*. Hospital transmission of multidrug-resistant *Mycobacterium tuberculosis* in Rosario, Argentina. *Medicina (B Aires)* 1996;**56**:48–50.
117. Katsoulidou A, Paraskevis D, Kalapothaki V, *et al*. Molecular epidemiology of a hepatitis C virus outbreak in a haemodialysis unit. Multicentre Haemodialysis Cohort Study on Viral Hepatitis. *Nephrol Dial Transplant* 1999;**14**:1188–1194.
118. Kakis A, Gibbs L, Eguia J, *et al*. An outbreak of group A streptococcal infection among health care workers. *Clin Infect Dis* 2002;**35**:1353–1359.
119. Boyce JM, Opal SM, Potter-Bynoe G, Medeiros AA. Spread of methicillin-resistant *Staphylococcus aureus* in a hospital after exposure to a health care worker with chronic sinusitis. *Clin Infect Dis* 1993;**17**:496–504.
120. Fawley WN, Wilcox MH. Molecular epidemiology of endemic *Clostridium difficile* infection. *Epidemiol Infect* 2001;**126**:343–350.
121. Morter S, Bennet G, Fish J, *et al*. Norovirus in the hospital setting: virus introduction and spread within the hospital environment. *J Hosp Infect* 2011;**77**:106–112.
122. Lin YC, Lauderdale TL, Lin HM, *et al*. An outbreak of methicillin-resistant *Staphylococcus aureus* infection in patients of a pediatric intensive care unit and high carriage rate among health care workers. *J Microbiol Immunol Infect* 2007;**40**:325–334.
123. Fisher GM, Kelsey MC, Cooke EM. An investigation of the spread of gentamicin resistance in a district general hospital. *J Med Microbiol* 1986;**22**:69–78.
124. Yoon YK, Sim HS, Kim JY, *et al*. Epidemiology and control of an outbreak of vancomycin-resistant enterococci in the intensive care units. *Yonsei Med J* 2009;**50**:637–643.
125. Kassis C, Hachem R, Raad II, *et al*. Outbreak of community-acquired methicillin-resistant *Staphylococcus aureus* skin infections among health care workers in a cancer center. *Am J Infect Control* 2001;**39**:112–117.
126. Lowe C, Willey B, O'Shaughnessy A, *et al*. Outbreak of extended-spectrum beta-lactamase-producing *Klebsiella oxytoca* infections associated with contaminated handwashing sinks. *Emerg Infect Dis* 2012;**18**:1242–1247.
127. Aumeran C, Baud O, Lesens O, Delmas J, Souweine B, Traore O. Successful control of a hospital-wide vancomycin-resistant *Enterococcus faecium* outbreak in France. *Eur J Clin Microbiol Infect Dis* 2008;**27**:106–114.
128. Pegues DA, Lasker BA, Mcneil MM, Hamm PM, Lundal JL, Kubak BM. Cluster of cases of invasive aspergillosis in a transplant intensive care unit: evidence of person-to-person airborne transmission. *Clin Infect Dis* 2002;**34**:412–416.
129. Arnold KE, Schweitzer JL, Wallace B, *et al*. Tightly clustered outbreak of group A streptococcal disease at a long-term care facility. *Infect Control Hosp Epidemiol* 2006;**27**:1377–1384.
130. Byers KE, Anglim AM, Anneski CJ, *et al*. A hospital epidemic of vancomycin-resistant enterococcus: risk factors and control. *Infect Control Hosp Epidemiol* 2001;**22**:140–147.
131. Marx A, Shay DK, Noel JS, *et al*. An outbreak of acute gastroenteritis in a geriatric long-term-care facility: combined application of epidemiological and molecular diagnostic methods. *Infect Control Hosp Epidemiol* 1999;**20**:306–311.
132. Xia Y, Lu C, Zhao J, *et al*. A bronchofiberoscopy-associated outbreak of multidrug-resistant *Acinetobacter baumannii* in an intensive care unit in Beijing, China. *BMC Infect Dis* 2012;**12**:335.

133. Zervos MJ, Kauffman CA, Therasse PM, Bergman AG, Mikesell TS, Schaberg DR. Nosocomial infection by gentamicin-resistant *Streptococcus faecalis*: an epidemiologic study. *Ann Intern Med* 1987;**106**:687—691.
134. Witte W, Braulke C, Cuny C, Heuck D, Kresken M. Changing pattern of antibiotic resistance in methicillin-resistant *Staphylococcus aureus* from German hospitals. *Infect Control Hosp Epidemiol* 2001;**22**:683—686.
135. Aldeyab MA, Monnet DL, Maria Lopez-Lozano J, *et al*. Modelling the impact of antibiotic use and infection control practices on the incidence of hospital-acquired methicillin-resistant *Staphylococcus aureus*: a time-series analysis. *J Antimicrob Chemother* 2008;**62**:593—600.
136. Aldeyab MA, Harbarth S, Vernaz N, *et al*. Quasiexperimental study of the effects of antibiotic use, gastric acid-suppressive agents, and infection control practices on the incidence of *Clostridium difficile*-associated diarrhea in hospitalized patients. *Antimicrob Agents Chemother* 2009;**5**:2082—2088.
137. Bertrand X, Lopez-Lozano J, Slekovec C, Thouverez M, Hocquet D, Talon D. Temporal effects of infection control practices and the use of antibiotics on the incidence of MRSA. *J Hosp Infect* 2012;**82**:164—169.
138. Vernaz N, Sax H, Pittet D, Bonnabry P, Schrenzel J, Harbarth S. Temporal effects of antibiotic use and hand rub consumption on the incidence of MRSA and *Clostridium difficile*. *J Antimicrob Chemother* 2008;**62**:601—607.
139. Polgreen PM, Yang M, Bohnett LC, Cavanaugh JE. A time-series analysis of *Clostridium difficile* and its seasonal association with influenza. *Infect Control Hosp Epidemiol* 2010;**31**:382—387.
140. Charvat H, Ayzac L, Girard R, Gardes S, Ecochard R. Detecting related cases of bloodstream infections using time-interval distribution modelling. *J Hosp Infect* 2010;**74**:250—257.
141. Birnbaum D. Analysis of hospital infection surveillance data. *Infect Control* 1984;**5**:332—338.
142. Haley RW, Bregman DA. The role of understaffing and overcrowding in recurrent outbreaks of staphylococcal infection in a neonatal special-care unit. *J Infect Dis* 1982;**145**:875—885.
143. Rushton SP, Shirley MDF, Sheridan EA, Lanyon CV, O'Donnell AG. The transmission of nosocomial pathogens in an intensive care unit: a space—time clustering and structural equation modelling approach. *Epidemiol Infect* 2010;**138**:915—926.
144. Rexach CE, Tang-Feldman YJ, Cohen SH. Spatial and temporal analysis of *Clostridium difficile* infection in patients at a pediatric hospital in California. *Infect Control Hosp Epidemiol* 2005;**26**:691—696.
145. Nuebel U, Nachtnebel M, Falkenhorst G, *et al*. MRSA transmission on a neonatal intensive care unit: epidemiological and genome-based phylogenetic analyses. *PLoS One* 2013;**8**:1.
146. Gandhi NR, Weissman D, Moodley P, *et al*. Nosocomial transmission of extensively drug-resistant tuberculosis in a rural hospital in South Africa. *J Infect Dis* 2013;**207**:9—17.
147. de Celles MD, Salomon J, Marinier A, *et al*. Identifying more epidemic clones during a hospital outbreak of multidrug-resistant *Acinetobacter baumannii*. *PLoS One* 2012;**7**:9.
148. Kumar VS, Pentland A, D'gata EMC. *Detecting clusters of multidrug-resistant Gram-negative bacteria (MDRGN) using space—time analysis in a tertiary care hospital*. 44th Annual Meeting of IDSA, Toronto 12th—15th October 2006. Abstract 269.
149. Kistemann T, Dangendorf F, Krizek L, Sahl HG, Engelhart S, Exner M. GIS-supported investigation of a nosocomial salmonella outbreak. *Int J Hyg Environ Health* 2000;**203**:117—126.
150. Kruger H, Steffen D. Hospital antibiotic resistance and GIS for visualization and early warning. *Abstr Intersci Conf Antimicrob Agents Chemother* 2002;**42**:447.
151. Kho A, Johnston K, Wilson J, Wilson SJ. Implementing an animated geographic information system to investigate factors associated with nosocomial infections: a novel approach. *Am J Infect Control* 2006;**34**:578—582.