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**Mathematical models of infection transmission in healthcare settings:
recent advances from the use of network structured data**

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ABSTRACT

Purpose of review

Mathematical modeling approaches have brought important contributions to the study of pathogen spread in healthcare settings over the last twenty years. Here, we conduct a comprehensive systematic review of mathematical models of disease transmission in healthcare settings and assess the application of contact and patient transfer network data over time and their impact on our understanding of transmission dynamics of infections.

Recent findings

Recently, with the increasing availability of data on the structure of inter-individual and inter-institution networks, models incorporating this type of information have been proposed, with the aim of providing more realistic predictions of disease transmission in healthcare settings. Models incorporating realistic data on individual or facility networks often remain limited to a few settings and a few pathogens (mostly MRSA).

Summary

To respond to the objectives of creating improved infection prevention and control measures and better understanding of HAI transmission dynamics, further innovations in data collection and parameter estimation in modeling is required.

KEYWORDS

Hospital-acquired infections; mathematical modeling; transmission; networks; systematic review

INTRODUCTION

Despite advances in biology and medicine, the burden of healthcare-associated infections (HAIs) has increased over the last decades [1]. Indeed, HAIs are the most frequent adverse event in health-delivery settings affecting up to one in three patients in intensive-care units (ICU) in developed countries [1]. The associated costs are estimated to be seven billion euros in Europe, and approximately six and a half billion dollars in the US [2-4], where 722,000 HAIs occur yearly in acute-care hospitals, resulting in 75,000 deaths [5].

The HAI burden stems notably from the emergence and spread of virulent infectious agents. Multi-drug resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenemase-producing *Enterobacteriaceae* (CPE), and viruses such as influenza, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome coronavirus and Ebola have become of concern for public health authorities in most countries [1]. Prevention measures such as hand-hygiene, isolation, antibiotic restrictions, staff cohorting and surveillance may significantly impact HAI rates, decreasing in particular MRSA and *Clostridium difficile* incidence by more than 70% [5].

Mathematical models have provided a theoretical framework for understanding complex transmission dynamics within healthcare settings for over 15 years [6-9]. Furthermore, they provide a quantitative approach to estimating the impact of various infection control strategies and their combined effects [6,7,9,10].

Over recent years, detailed data informing on the interactions between patients and healthcare workers (HCWs) or patient transfers within and between healthcare settings have been integrated in such models. Patients transfers between hospitals have been increasingly studied [11], as well as data on contacts between patients and healthcare workers (HCWs), in particular, digital trace measuring face-to-face proximity [12,13] or individual movements [14].

Here, we conduct a systematic review of mathematical models in healthcare settings using such real data on networks within institutions and between institutions. We present an overview of the methodological specificities related to the integration of network data in the different modeling studies and we study how they may improve our understanding and predictive capacity of HAI spread in healthcare settings.

METHODS

We conducted a systematic search in three different databases: (1) MEDLINE (1946 to present), (2) Web of Science Core Collection (1956 to present), and (3) Institute of Electrical and Electronic Engineers (IEEE) Xplore Digital Library (1893 to present). Results included all articles published until January 26, 2017, the final day of the search. All results from the search query were independently screened by two reviewers for inclusion criteria eligibility and selection after review of titles, abstracts, and then full texts. Query structure, inclusion and exclusion criteria can be found in Appendix 1 and 2.

We defined four lists to classify our selection results:

- L: all studies meeting our first two inclusion criteria comprising of all mechanistic models of pathogen transmission within healthcare settings. We use the term “HAI” in a generic and inclusive way to encompass multidrug resistant organisms such as MRSA, ESBL producers, influenza, and VRE among other pathogens.
- L_1 : all studies from list L incorporating real contact data (within institutions)
- L_2 : all studies from list L incorporating real transfer data (between institutions and/or wards)
- L_3 : all studies from list L that incorporate explicit contact or transfer network structure in healthcare settings without real data

All studies using real data (L_1 and L_2) were analyzed regarding various characteristics such as pathogen studied, data sources, and model parameters. We also compared L_1 and L_2 models characteristics with L models characteristics using Fisher exact and Chi^2 statistical tests.

RESULTS

Our search retrieved a total of 5653 distinct records from the three databases (Figure 1). After screening titles and abstracts, a total of 216 studies were selected for list L, including eight papers added through reference searching. From this list, we identified a total of 28 models using intra-hospital contact data (L_1) [15-40,41*,42*], 26 models using inter- or intra-hospital transfer data (L_2) [43,44**,45-58,59*,60-66,67**,68], and 22 contact or transfer network healthcare models without real data (L_3) [69-90].

Publication Trends

Publication of mathematical models of pathogen spread in healthcare settings has greatly increased in recent years (Figure 2) ($p < 10^{-11}$, Spearman's rank correlation). The first models including real network data were published in 2002 and used directly observed within-hospital data on inter-individuals contacts [31,34]; the first model including data on inter-facility transfers was published in 2007 [47]. From these first publications on, the number of yearly published L_1 ($p = 0.03$, Spearman's rank correlation) and L_2 ($p = 0.02$, Spearman's rank correlation) models have been increasing. Overall, since 2002, L_1 and L_2 models represent 27% of L models, with an increasing portion of L_2 models (Suppl Figure 1).

Pathogens studied and epidemic situations

MRSA was the most studied pathogen in L_1 and L_2 models (44.1%) followed by: influenza (13.6%), vancomycin-resistant *Enterococci* (8.5%), HAIs in general (8.5%), *C. difficile* (5.1%) and CPE (5.1%) (Figure 3). The distribution of pathogens studied in L_1 and L_2 models did not differ significantly from that observed in all models ($p = 0.09$, Fisher exact test).

In general, L_1 and L_2 models either simulated outbreaks of these pathogens in a susceptible population or assessed the impact of long-term infection prevention and control on the ongoing epidemic of prevalent HAIs.

Healthcare settings

Out of 54 L_1 and L_2 models, 49 (91%) took place in acute-care settings (Table 1A). The mean number of healthcare settings in general included in the models was 122 [range: 1-3306], with a median at one of L_1 and at 98 of L_2 models. Ward-level description of HAI spread was present in 35% of publications (19/54), of which most modeled one intensive-care unit (Table 1B). Only Karkada et al.'s study was an outlier, analyzing a total of 3306 ICUs in the US [58]. L_1 models had a median study size of 100 patients [range: 2-3329] and 34 HCWs [range: 1-19508]. L_2 models incorporated a median of seven million transfers [range: 130,000-13 million].

Data sources

All transfer data were collected using electronic patient records such as national medical and surveillance registers [43,53,54], hospital discharge summaries [45,47-49,51,60,62,65], or insurance databases [58]. Data used to collect the contact patterns between patients and HCWs came from four main sources: (1) shadowing – direct observation of interactions between patients and HCWs –, (2) surveys, (3) medical records and (4) individual wireless proximity sensors recording the identity of other sensors located in a close area. Historically, between 2002 to 2006, shadowing was the first source of data on contact networks in healthcare settings (Figure 4) [20,31,32,34,37]. During the period 2007-2011, new methods of contact data collection appeared such as medical records [19,25,28] and surveys [17,18,38,40,41*]. Finally, following technology innovations, proximity sensors were introduced in four studies published over the period 2012-2016 [24,35,36,42*].

Types of models

L_1 and L_2 models were mostly agent-based, rather than compartmental (43 vs. 12 models), and stochastic, rather than deterministic (53 vs. 4 models) [39]. These were significant differences with L models ($p < 10^{-5}$, Chi^2 test).

Model Objectives

L_1 and L_2 models all aimed at either assessing control interventions or better understanding HAI spread and the impact of social networks. Inclusion of data on social networks allowed simulating more innovative and realistic infection prevention and control strategies, including heterogeneous hand-hygiene compliance or cohorting levels [16,19,22,27,31,32,34,35]. Hand-hygiene compliance was the most common intervention studied [20,22,27,29,31,34,35,37,39,40,41*,46,56], along with antibiotic exposure [32,33], targeted or screening of patient groups or universal screening of all patients at admission [48,51,57], isolation [26,46,57], and HCW vaccination [17-19]. Other models explored the role of patient-HCW interactions through variations in cohorting by modifying patient: HCW ratios [16,31,34], social interactions in hospitals [24,28,36], and hospital system-wide spread and control through patient movement [45,47-50,59*,60-66]. In addition, data on transfers within a healthcare network gave insights into sentinel selection for development of more effective sentinel surveillance systems [43,50,55,58] and supported improved coordinated regional control [23,45,59*,61,68]. Finally, some models explicitly assessed the underlying network structure of interactions through social network analyses of patient flows in hospitals [19,23,30,35,87,89] and between hospitals [50,53-55,58,64,65].

Parameter Estimations and Model Cross-Validation

Around 17% of L_1 or L_2 papers included model parameter estimation using observed infection or colonization data, rather than simple calibration or using values from the literature. Model predictions were rarely cross validated with independent data-sets (eight publications overall). In these aspects, L_1 and L_2 models did not differ from L models in general.

DISCUSSION

Mathematical models of infections in healthcare settings have become more frequent over the years. This increase may be due to multiple factors including perceived usefulness of models as tools for understanding the impact of infection prevention and control in the health field, for understanding drivers of recent major epidemics such as the 2002-2003 SARS outbreak [15,78,91,92] and the 2014-2015 Ebola epidemic [42*,93-95], or growing awareness of factors contributing to the global impact of antibiotic resistance [96]. In parallel, increased availability of digitalized medical records or surveys, and development of sensor technology to monitor inter-individual contacts provide researchers with the means to build more realistic models.

Review scope and limitations

In this systematic review, we conducted an exhaustive search of articles studying pathogen spread in healthcare settings through mathematical modeling. Using complementary databases (PubMed, Web of Science, and IEEE Xplore Digital Library) was important and necessary to find the articles analyzed in this review.

However, this review was subject to some limitations. Given that the scope of this review involves both health sciences and computational biology, we could have included more databases in the computer science field. In addition, we only considered publications in English and French, which may have limited the variety of country settings. Statistical models were excluded because they did not meet the objective of the review; however, these models may also improve the understanding of transmission dynamics of pathogen spread in healthcare settings.

Main results of the review and implications for future work

Several points which have been raised by our review may lead to recommendations for future modeling work. The range of pathogens, settings, and situations explored by models based on

real data on networks of individuals or facilities remains to this day highly restrictive. Hence, the increased realism in the description of social networks is counterbalanced by the current limitations in the range of investigated questions.

First, 80% of L_1/L_2 models were set in a four developed countries (the US, UK, the Netherlands and France), while L models considered a wider variety of countries (Suppl Figure 2). This can be explained by their use of more advanced data management technologies, resulting in a better availability of relevant data, as well as by the presence of a very active community of modelers. However, healthcare-associated infections also represent a major issue in developing countries, mainly due to high antimicrobial resistance levels and difficulties to afford second-line treatments [97]. Future work should take these settings into account.

Secondly, the most studied pathogen was MRSA, followed distantly by influenza, HAIs in general and vancomycin-resistant enterococci. Although this was true of all models of HAI spread, the domination of MRSA was even stronger in models incorporating data on observed networks. This may be explained by the large amount of available epidemiological data on MRSA in healthcare settings, reflecting the historical importance of MRSA in HAIs. In addition, data on MRSA carriage are easily collected from nasal or other surveillance swabs, while other pathogens such as *Enterobacteriaceae* require rectal swabs, which can be more difficult to obtain. While MRSA has indeed represented a major threat over the last decades, the incidence of MRSA infections currently seems to be declining in most developed countries, [97] yet other multi-resistant bacteria such as ESBL-producing *Enterobacteriaceae* become more prevalent [98,99]. Future models should definitely consider a wider range of pathogens.

Thirdly, the vast majority of L_1 and L_2 models were set in acute-care settings, with most ward-level descriptions taking place in ICUs. ICUs are frequently modeled because of their

high risk of HAIs, raised by a high number of invasive procedures in critical-state patients, and require well-informed recommendations regarding control interventions. Consequently, research funding in ICUs is more prevalent and both data collection and implementation of control interventions are facilitated by better informed ICU HCWs compared to other wards. However, HAIs are also an issue in other types of hospital wards, in which lower HCW-to-patient ratios and decreased risk awareness may lead to HAI outbreaks. On the health systems-level, the majority of L_2 models described networks of hospitals linked by their shared patients; only a few recreated transfer networks between the wards of a given hospital in order to study how the impact of infection prevention and control interventions may vary depending on hospital ward specialties [46,51]. Intra-hospital spread has been shown to be one of the major reasons for transmission of SARS in Toronto, Canada, and Taiwan and MERS-CoV in Alhasa, Saudi Arabia, and Korea.[100-102] Future research should attempt to include ward-level modeling as it provides more specific and realistic patients and HCW interactions that are overlooked when modeling at the hospital level, and take into account wards other than ICUs.

Additionally, models of HAI spread in settings outside acute-care should be developed. For instance, the importance of nursing homes in the overall spread of HAIs has been underlined. Factors such as long length-of-stay of nursing home residents have been shown to play an important role in both driving sustained endemics of infections and increasing the risk of epidemics in entire healthcare networks [44,60,63]. Similarly, the impact of transmission in [28] or readmission from [47] community settings on HAI transmission in healthcare settings is rarely assessed among models using real data. Research should focus on modeling nursing home and community settings with collected data to better understand the complexity of interactions within healthcare networks and their impact on transmission dynamics in healthcare settings.

Another important issue is the inclusion of observed colonization or infection data in modeling works to calibrate or validate model predictions. Although models incorporating data on inter-individual contacts or patient transfers are more likely to have access to patient medical records or disease status from healthcare workers, parameter estimation and model validation using colonization or infection data remains rare overall. A major objective of future research should be to include observed infection or carriage data collected simultaneously with the network data, among the same individuals. Another benefit of simultaneously collecting contact or transfer data and infection data would be the possibility of assessing the pertinence of network data to help predict HAI spread. Indeed, while most published models using network data implicitly assume that inter-individual contact and/or inter-facility patient transfer networks drive HAI spread, other factors may impact pathogen diffusion in healthcare settings. Depending on the involved pathogen, environmental contamination for instance may play a major part. It is therefore of the utmost importance to further investigate what portion of the pathogen-specific diffusion risk may be explained by network data [24].

Conclusion

Our review assessed the use of contact and transfer network data in models over time and its impact on understanding infection transmission dynamics in healthcare settings. Models incorporating such data were limited to a small number of countries, settings, and pathogens, while there is a steady emergence of network graphs to study the contact and structure of patient movement and interactions with HCWs. These models give new insights into more effective HAI prevention and control strategies in both endemic and epidemic situations. Further innovations in data collection and use in modeling are required to improve understanding of transmission dynamics to reinforce existing recommendations and evaluate new control strategies.

Key Points

- Mathematical models of infections in healthcare settings have become more frequent over the years
- Increasing trends of models based on real data on networks of individuals or facilities are due to perceived usefulness as tools for infection prevention and control, increased availability of digitalized medical records or surveys, and development of sensor technology
- The range of pathogens, settings, and situations explored by these models remains to this day highly restrictive which may reflect limited data availability, historical importance of certain infections (i.e. MRSA), and high-risk HAI settings that require more intensive HCW training and precautions (i.e. ICUs)
- The main contributions of models in terms of using real data on networks are to develop more innovative and realistic HAI control strategies and to better understanding the impact of social networks on HAI spread

Definitions

- Compartmental model: a model where a population is sub-divided into groups corresponding to a status. For example, the SIR model is a basic compartmental model composed of three groups of people with the following status: susceptible, infected and recovered. Each compartment contains a certain number of people from the population presenting the status.
- Agent-based model: rather than grouping people in a compartment in terms of their status, the agent-based model studies each individual separately. These models commonly study the connections between individuals (patients and/or HCWs) with

each other in terms of a shared environment (ward, room) or through their contacts (direct, indirect).

- **Deterministic model:** a model in which the output is fully determined by the initial conditions and parameter values (usually a compartmental model formulated using differential equations)
- **Stochastic model:** a model including inherent randomness, in which, for a given set of initial conditions and parameter values, an output distribution is provided to account for uncertainty in predictions (often used for small populations in which random fluctuations are important)
- **Social network:** a network with components and links, and within the scope of our review, they are either contact networks of healthcare workers (nurses, physicians, etc.) and patients or of hospitals that are linked by their patient transfers.
- **Social network analysis:** in the case of our review, it is the assessment of the contacts or healthcare system structures which can help identify “super-spreaders” that are highly linked and have the most potential to spread disease in the network

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Conflicts of interest

We declare that we have no competing interests.

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In this study, hand hygiene compliance and contact precautions are evaluated using a Ross-Macdonald model to describe the transmission and control of CRE in an ICU. The authors estimated the parameters including the per capita contact rate, probability of HCW colonization (with and without contact precautions), and HCW compliance to control measures from the ICU's observed collected data.

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FIGURE LEGENDS

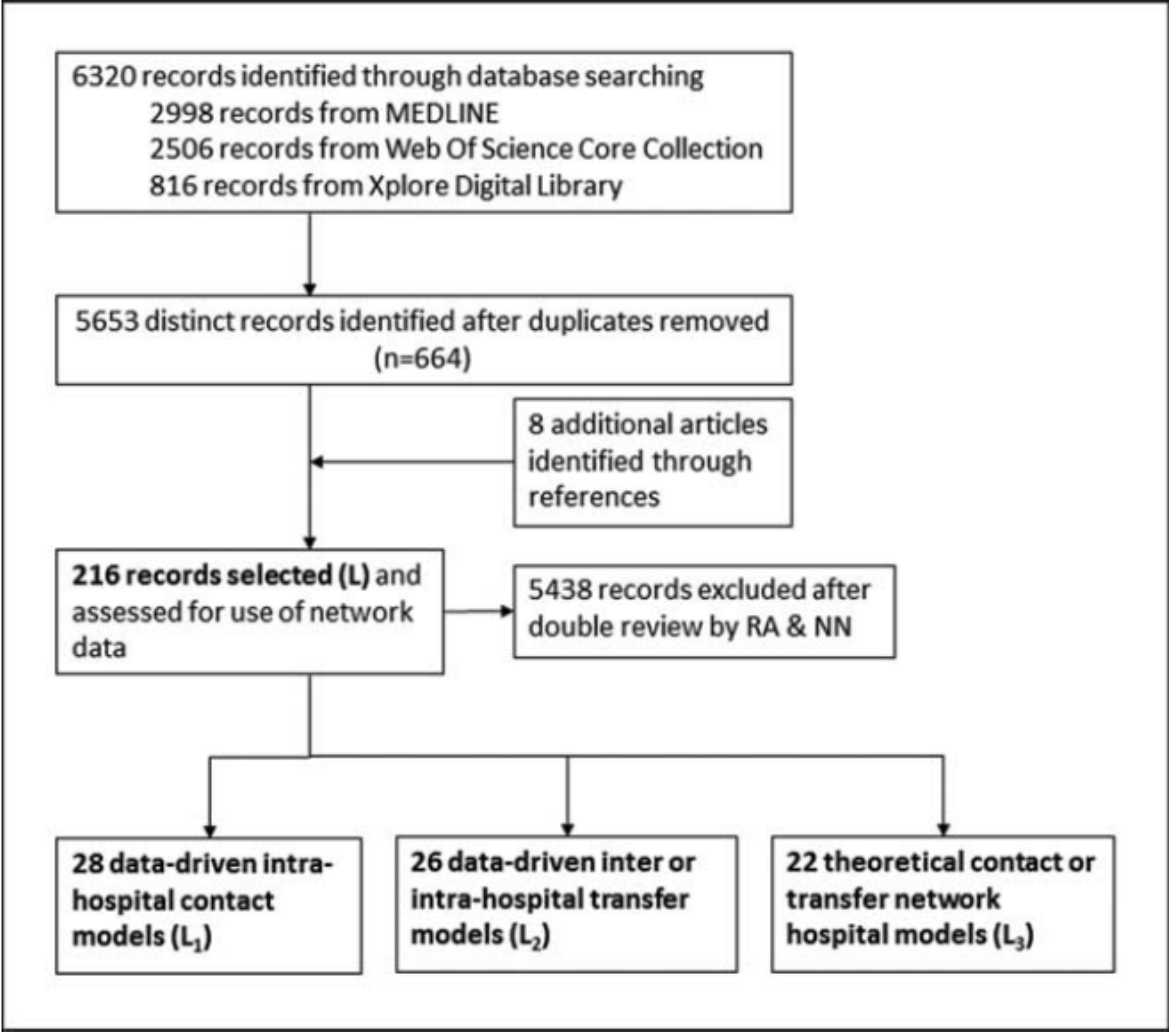


Figure 1. PRISMA diagram reviewing literature sources for mathematical models that examined the transmission dynamics in healthcare settings.

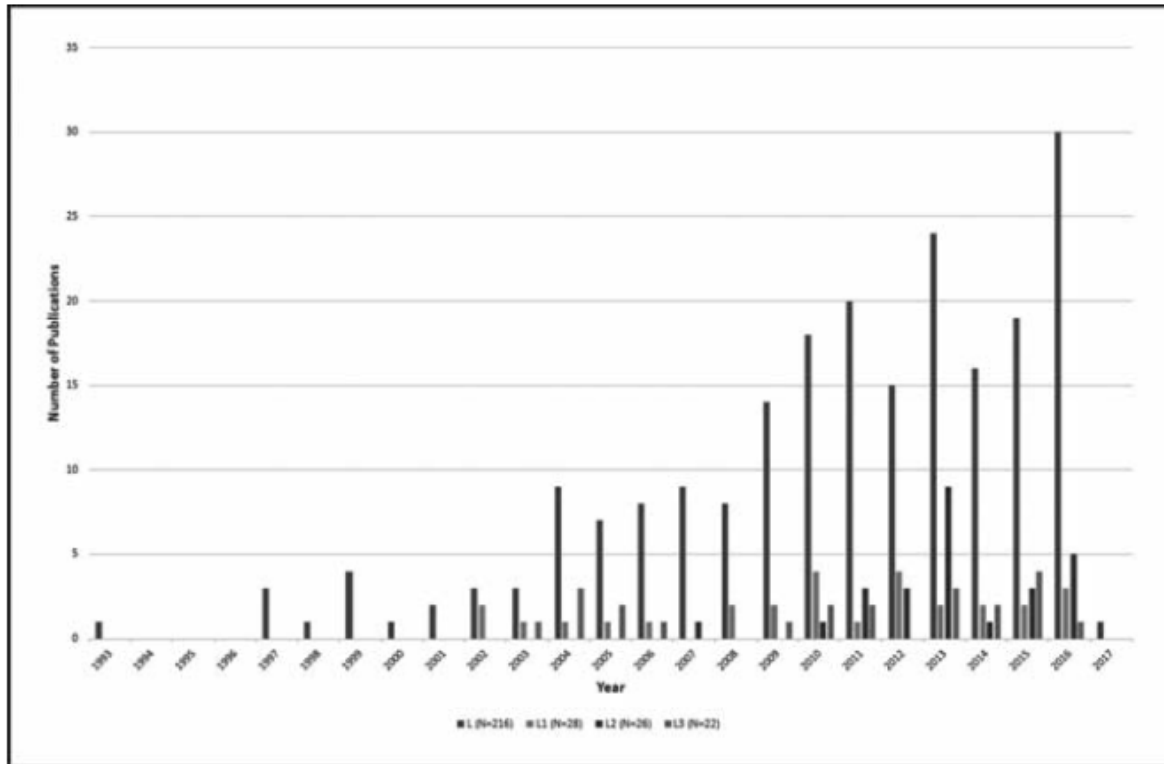


Figure 2. Number of mathematical models of HAI spread in healthcare settings published over time. The total of all models published (L, in red), those using real contact data (L_1 , in green), those using real transfer data (L_2 , in purple), and those focusing on the impact of social networks without real data (L_3 , in blue) are depicted.

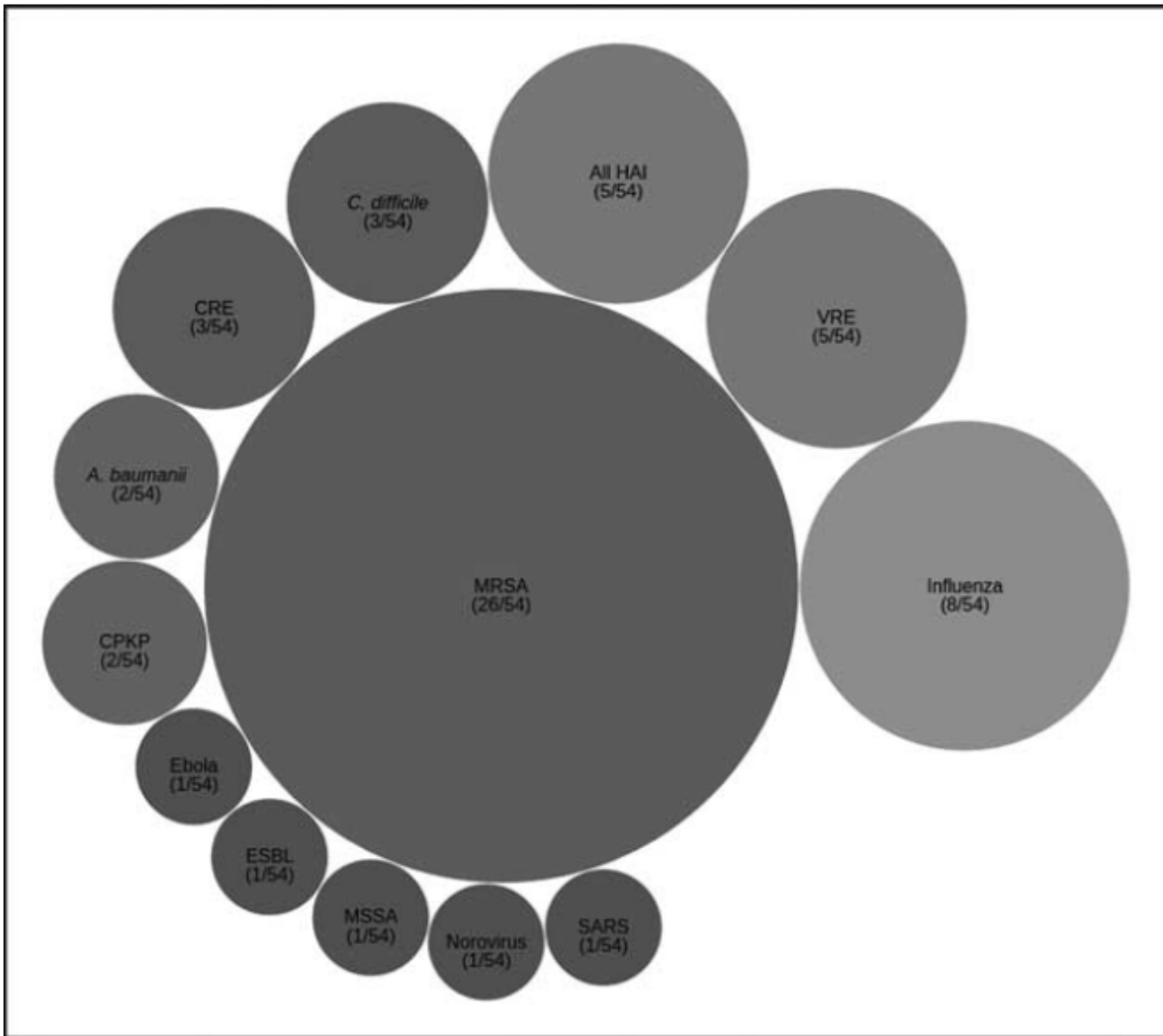


Figure 3. Pathogens modeled in models using real contact (L₁) or transfer data (L₂).

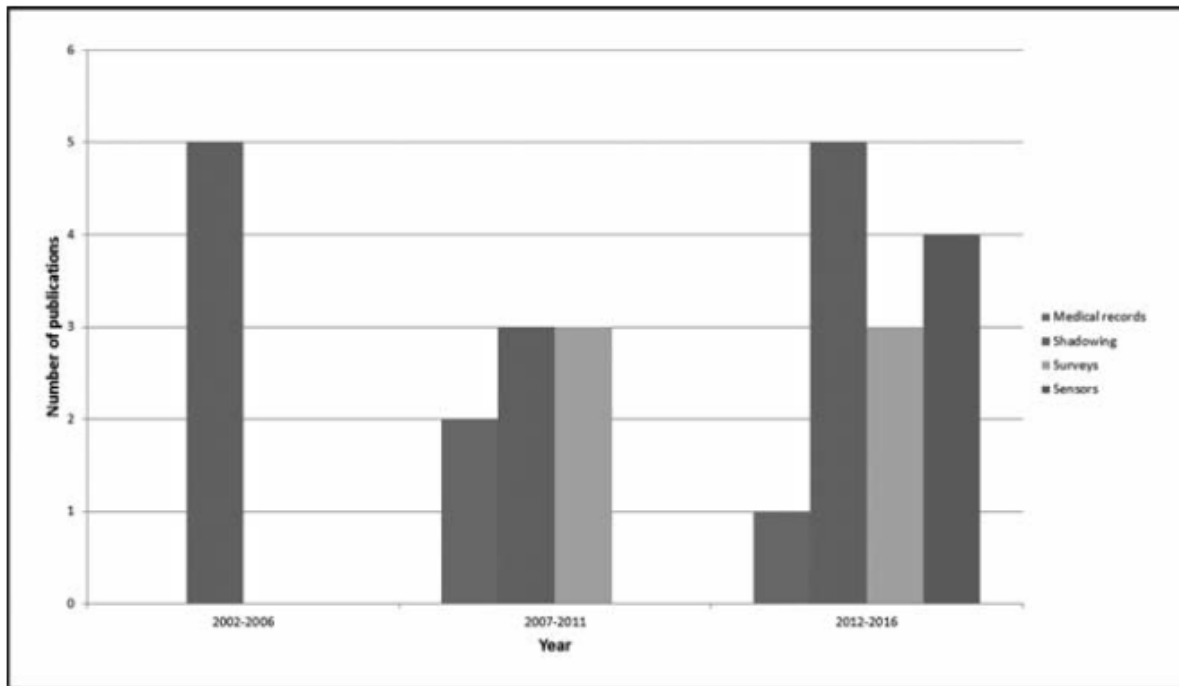


Figure 4. Contact data collection sources in models using real contact data (L_1): changes over time.

Supplementary Figure 1. Proportion of mathematical models of HAI spread in healthcare settings that include real network data published over time. The proportion of the total number of published models represented by those using real contact data (L_1 , in green), those using real transfer data (L_2 , in purple), and those focusing on the impact of social networks without real data (L_3 , in blue) is depicted for four time periods: 2001-04, 2005-08, 2009-12, and 2013-16.

Supplementary Figure 2. Country of study of the models using real contact (L_1) or transfer data (L_2).