Simulation models for transmission of healthcare-associated infection: a systematic review

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Background

Healthcare associated infections (HAIs) pose a serious risk for patients and providers as they cause increased morbidity and mortality, prolonged length of stay in healthcare facilities, increased prevalence of multi-drug resistant organisms and psychological and financial burdens to patients, their families and the healthcare system. The risk of HAIs is universal and pervades every healthcare facility, setting and system globally. In Europe, the prevalence of HAIs was estimated at 5.5% (1) and about 2.6 million new patients having HAIs have been identified annually (2). These infections accounted for an estimated 33,000 attributable deaths and 900,000 disability-adjusted life-years (3). In the US, the estimated prevalence of HAIs in hospitals was between 2.9% and 3.5% in 2015 (4). The burden is even higher in low- and middle-income countries (LMICs). A systematic review and meta-analysis reported that the pooled prevalence of overall HAIs in Southeast Asia, where most countries are middle-income, was 9.1% (5). The reported prevalence in Africa varies significantly: in Ghana, prevalence ranged between 3.5% and 14.4% in acute care hospitals, and in tertiary hospitals in South Africa and Ethiopia it was 7.67% and 19.4%, respectively (6-8). Data on the impact of HAIs at the national level in LMICs, especially African countries, is scanty and fragmented, generating difficulty in assessing the true scale of the problems of HAIs. The actual figure is assumed to be higher due to the lack of a functioning HAI surveillance system in these countries (9).

Historically, randomized control trials (RCTs), cohort studies and case-control studies were commonly used methods to investigate the epidemiology of diseases in general and the epidemiology of HAI in particular (10). Additionally, researchers performed cluster RCTs or quasi-experimental studies to examine the

effectiveness of various measures for infection prevention and control (IPC) (11). However, performing large cluster RCTs across various health facilities to achieve generalizability and sufficient power to address important research questions is difficult. Furthermore, although quasi-experimental studies are more feasible and practical to conduct, lack of randomization is a threat to the internal validity and limit the generalizability of the results to larger populations (11). Although simpler non-mechanistic modeling approaches such as statistical models and analytical models have also been used to evaluate IPC interventions, they cannot capture the complexity and dynamics of HAI transmission and the healthcare contexts in which the interventions are implemented. Therefore, a more comparable, reliable and easy-to-use planning tool is needed to assess interventions and their impacts (12).

Modeling is increasingly being used to improve understanding of epidemiological patterns of HAIs and to facilitate decisions on intervention prevention and control (IPC). Mechanistic simulation modeling that captures the dynamics between patients, pathogens, and the environment is particularly useful for studying complex systems like the healthcare system (13). A simulation model can be used to understand the dynamics of HAIs and IPC and how various complexities influence these dynamics or to predict outcomes of IPC interventions. The latter can only be done credibly provided we understand the system well enough. Simulation modeling provides a risk-free environment where ideas on IPC strategies can be tested in a systematic manner without the time, costs and risks associated with experiments conducted in a real-world setting. It is a valuable tool to guide the selection of the most appropriate empirical research to pursue and to examine the effects of IPC strategies, serving as a “virtual policy laboratory” for decision support by researchers, policy makers, public health officials, hospital managers and administrators, and other health care decision makers (14).

Like other modeling methods that try to predict outcomes, simulation modeling does not necessarily provide precise results that are completely reliable (e.g., the exact number of infections or the precise course of an epidemic). Perfect prediction using simulation can rarely be achieved as it is impossible to build a model that fully replicates the real world; particularly when we describe a stochastic system as complex as infection transmission, which is influenced by human behaviour, pathogen and host biological characteristics, and the health facility structure among many factors. Nonetheless, simulation modeling can help understand

the relative effectiveness of different interventions, identify the risk of HAIs for different population groups, provide confidence intervals on the epidemic behaviors and, therefore, aid decision making. IPC decision-makers using simulation models for decision-support must consider model assumptions and their relevance to the particular context in addition to carefully weighing the predicted benefits of interventions against the inconvenience, stigmatization, and costs they might engender.

A number of reviews have been conducted on mathematical modeling of HAIs in the 21st century. Grundmann and Hellgriegle wrote the first literature review on HAI modeling in 2006; they focused on explaining the capacity of models to enhance epidemiological understanding in hospitals, and thus their work was restricted to the detailed description of a number of publications (15). Nelson and his colleagues (2017) recently carried out a similarly in-depth and limited in breadth literature review on economic analysis applied to HAIs using dynamic transmission models (16). In contrast, van Kleef et al. (2013) published a systematic review on the overall trends in application and development of mathematical models of HAIs over time (17). Lastly, Opatowski et al. (2011) illustrated the overall progress of mathematical and simulation modeling of multi-drug resistant bacteria spread in both the community and hospital settings (18).

Since these reviews were conducted, a significant number of simulation models, including agent-based models (ABM) and hybrid models, exploring the dynamics of HAIs have been published. The application of simulation modeling of HAIs has grown rapidly, possibly due to the recognition of this method's advantages and the increasing capabilities of computers. The current adoption and application of HAIs simulation modeling need to be consolidated and updated to facilitate further development of appropriate models, enabling the investigation and evaluation of the best practice for IPC under different healthcare settings from clinical and economic perspectives. Therefore, we conducted a systematic review to establish a) how simulation models have been utilized to investigate HAIs and their mitigation, b) how these models have evolved over time, and to identify c) gaps in their adoption and d) useful directions for their future development.

Reviewed Simulation Modeling Types

System Dynamics (SD) – A top-down continuous simulation modeling method which characterizes the structure of dynamic and complex systems, using stocks, flows, feedback and delays within such systems to explore how the system structure determines the system behavior (19). Stocks (or "levels") are defined as aggregation or accumulations of inflows and outflows over an interval of time. Flows (or "rates") change a stock over time by adding to (inflows) or subtracting from that stock (outflows). SD models are well-known for their ability to depict non-linear relationships which derive from the existence of feedback processes that exist where actors within a system will later be affected by their actions (19). In this review, we also consider compartmental models from the mathematical epidemiology and ecology literature that describe the disease transmission dynamics and link them to aspects of healthcare facilities and provision of services that effect outcome. These models similarly take a top-down approach that often assumes continuous time, and they are implemented using differential equations (20).

Discrete Event Simulation (DES) – A process-based simulation method used for modeling the operation of a system as a discrete sequence of activities and events in time, characterizing and analyzing queuing processes and networks of queues, and solving problems of resource utilization (21). Events, entities, attributes, and resources are the key components in DES. Entities are passive individual objects that possess attributes. These attributes are unique characteristics or features such as age and health status. Resources, as defined in DES, require time to provide a service to an entity, making other entities wait and form a queue. Entities consume resources while they experience events. However, the consumption of those resources does not depend on individual-level entity behavior. As entities use up resources they are indirectly competing with other entities in the queue (22). DES allows for capturing the effect of variability, stochasticity, and randomness of multiple elements within a system, but it does not explicitly model feedbacks or interactions between entities (23).

Agent-Based Model (ABM) - A bottom-up simulation method for modeling dynamic and adaptive systems with autonomous entities called agents and their environment (24, 25). The agents are described by their properties, actions, decision rules, and possibly goals, and they interact with one another and the environment. They live in the environment and sense it. They decide what action to employ at a certain time on the basis of their own state, their own defined decision rules and the environment state (including

other agents with which they interact). Agents can have explicit targets to minimize or maximize, and they can also learn and adapt based on experience. Agent-agent and agent-environment interactions result in the update of agents' internal state or decision on their next actions. Similarly, the environment's state can update. As agents and the environment interact and evolve or potentially co-evolve, micro- and macro-level patterns emerge. We also view similar microsimulation and individual-based models from the mathematical epidemiology and ecology literature as ABMs in this review, though in these models the entities are often only reflexive and do not make autonomous decisions.

Hybrid simulation models – A simulation modeling method that combines the methodological strengths of at least two different simulation modeling methods (26). We describe a number of designs for hybridizing simulation models based on work by Morgan et al. (2017) (23).

- *Sequential design* – A design for combining two or more simulation modeling methods that can capture different parts/behaviors of the same system or at different levels of detail. The simulation models that are hybridized interact with one another in a way that information or data is passed from one model to the next model.
- *Enrichment design* - A design for combining two or more simulation modeling methods to form a single model in which one method remains the core method that defines the system and other enhancing methods are transferred into and embedded within the primary method.
- *Integration design* – A design for combining two or more simulation modeling methods to form a single model which presents one coherent and concise view of the system, and captures interactive influences within the system.
- *Interaction design* - A design for combining two or more simulation modeling methods in which individual models can operate independently but work together to capture interactive influences within the system.
- *Parallel design* - A design for combining two or more simulation modeling methods that provide two potential representations of the same system, offering complementary insights of the system.

Table 1 provides an overview of the assumptions, inputs, outputs, and data dependency for each simulation modeling method. Other studies compare different aspects of these simulation methods more generally

than in HAI but in greater detail, including Parunak et al. (1998), Phelan (1999), Schieritz and Milling (2003), Borshchev and Filippov (2004), Rahmandad and Sterman (2008), Siebers et al. (2010), Scheidegger et al. (2018) (25, 27-32).

Table 1: An overview of the assumptions, inputs, outputs, and data dependency of SD, DES, and ABM

	SD	DES	ABM
Assumptions	Entities within each stock are mixed homogeneously; simulation is deterministic.	Entities are passive and do not interact with one another or learn from or adapt to the environment, but they can be heterogeneous; simulation is stochastic.	Entities can be heterogeneous and autonomous decision-makers, who can learn and adapt to their environment; entities can interact with each other; simulation is typically stochastic.
Inputs	Stock and feedback and accumulation structures; initial levels of stock/sub-populations aggregated by particular characteristics; rates which characterize the inflows and outflows of a stock.	Structure of queuing network; types of entities and resources (e.g., HCWs, hospital beds, and equipment), and their characteristics; time between entity arrivals, and number of entities per arrival; service time or delays.	Agent types and definitions in terms of their characteristics, possible actions and rules of behavior; initial number of agents; environment characteristics and rules; definition of agent-agent (e.g., network), agent-self, and agent-environment interactions.
Outputs	Deterministic time-series of population/stock levels and flows and insight into behaviour of the system.	Stochastic time-series of, and insight into, operational performance outputs such as queue lengths, utilization of resources, and frequency of events; tracking of individual entities.	Stochastic (typically) time-series of population and sub-population outputs such as number of entities in a specific state, frequency of actions, and frequency of events as well as state of the environment; insights into the system emergence behaviour; tracking individual entities.
Data Dependency	Objective data at aggregate levels supplemented by judgmental, subjective data and informational links	Depending on simulation aims, these methods can be highly data-dependent as they model entities at the individual level and try to describe variations in their characteristics and other inputs.	

Methods

Information Sources and Search Strategy

Pubmed, EMBASE, Cochrane Library, ABI/INFORM Collection via ProQuest, Business Source Complete and Scopus were searched from the date of inception to the 19rd of February 2019. Results were restricted to peer-reviewed publications written in English. Search terms for healthcare-associated infections were combined with search terms for simulation models as follows:

- *Infection OR infections*

AND

- *Health care associated OR hospital acquired OR nosocomial OR HAI* OR HCAI**

AND

- *System dynamic* OR compartmental OR agent based OR microsimulation* OR discrete event* OR simulation**

All databases were searched identically. The detailed search strategy for each database is in Appendix A. Reference lists of the previous literature reviews (15-18) were also searched for relevant citations.

Eligibility Criteria

We included studies which had fulfilled all of the following criteria: 1) simulation modeling of the dynamics of HAI transmission, clinical and economic evaluation of preventions for HAIs, and/or the dynamics of antimicrobial resistance; 2) simulation models including SD, DES and/or ABM; 3) a primary focus on HAI transmission in healthcare settings including hospitals, long term care facilities (LTCFs) (e.g., nursing homes, and care homes) and/or medical centres.

Exclusion Criteria

We excluded studies which did not involve: either 1) human-to-human transmission; or 2) human-environment-human transmission, or did involve: 3) animal transmission of HAI; or 4) pharmacokinetics and/or pharmacodynamic of antimicrobial drugs and/or molecular biological perspectives within host (e.g., molecular mechanisms of antibiotic resistance within host, efficacy and/or side effects of antibiotics, mode

of action of drugs); or 5) within host immunity or strain competition only; or 6) community transmission of pathogens spread in the healthcare environment as well, where the focus of the papers was community spread (e.g. SARS epidemics); or 7) literature review which did not contain new primary studies. Furthermore, we did not include editorials or letters to editors.

Data Collection Process

Data was extracted for the included studies, categorized and summarized in tabular format (Table A1 in Appendix A).

Data Items

We extracted key data to answer the objectives of this review. Firstly, this contained the basic information of the studies (study title, authors, year of publication). Secondly, as the main purpose of the review was to explore the existing use of simulation modeling for understanding HAI transmission and improving IPC in various healthcare settings from clinical and economical perspectives, we looked for the following codes: country of research, setting, type of simulation model, research theme, aim of the simulation model, pathogen, and inclusion of economic analysis. Additionally, because we were interested in how models of HAI transmission in healthcare settings were simulated to evaluate the effectiveness of IPC strategies, data on the type of intervention and the type of interactions (i.e., patient-healthcare worker (HCW), HCW-HCW, patient-patient, patient-visitor, environment reservoir for transmission, interaction between health facilities and interaction between health facility and community) were also extracted. Furthermore, to explore how different types of simulation models and hybrid models have been utilized, we looked into technical perspectives of these models which included whether sensitivity analysis, software used for simulation, calibration, validation and verification, transferability and generalizability were performed and how they were performed.

Results

Study Selection

Figure 1 shows the process of identification, screening and selection using the PRISMA flowchart (33). There were 606 records identified from electronic database searches and 25 records from other sources.

After removing duplicates and reviewing the title and abstract of the remainder, full-text articles were retrieved for the retained 109 records to assess their eligibility. Further 54 records were removed as they either did not meet the inclusion criteria. An additional 13 studies were identified via reference screening of the existing systematic reviews (15-18). Overall, 68 publications were included and reviewed in detail.

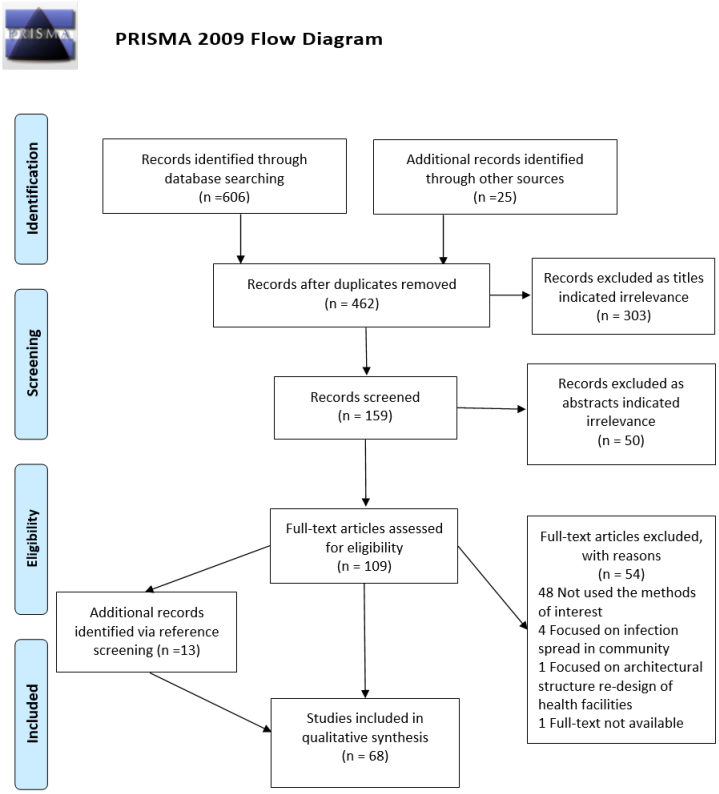


Figure 1: PRISMA Flow Diagram

Causative Organisms Modeled

Almost half of the included studies investigated the dynamics of Methicillin-resistant *Staphylococcus aureus* (MRSA) in a healthcare setting (47%, 38 studies) followed by Vancomycin-resistant *Enterococci* (VRE) and *Clostridium difficile* (CD) with significantly less studies (12%, 10 studies and 7%, 6 studies respectively). Other pathogens have rarely been the subject of interest for studies in this field.

Country of Research

A quarter of the publications did not specify a particular country. Of the studies that did specify a particular country: only two (3%) looked at healthcare setting in a middle-income country (South Africa and Thailand) and another three (4%) looked at an upper middle-income country (China). The majority of publications (68%, 46 studies) concentrated on HICs of which nearly half were the US (21 studies).

Types of Simulation Model

SD models accounted for 38% of the simulation models (26 studies). The first SD model of HAIs was developed in 1997 (34) while ABM and DES models of HAIs were only introduced in 2005 and 2006 respectively (i.e., nearly 10 years later) (35, 36). Although ABM and DES models of HAIs were introduced nearly concurrently, ABMs were used much more frequently to model HAIs than DES, and they accounted for more than a third of the reviewed models (38%, 26 studies).

Model Hybridization

Hybrid model use has increased since they were introduced in 2007 (37). Thirteen percent of the included studies (9 studies) adopted hybrid models which combined two types of simulation modeling (37-45). Based on a toolkit of designs for hybridizing two types of simulation modeling proposed by Morgan, Howick and Belton (2017) (23), we identified that six studies mixed ABM and SD models using either the enrichment (38), interaction (39) or integration (40, 44, 45) approach. Two studies adopted a sequential design to combine SD and DES (42, 43) and one used a SD model and a stochastic continuous time Markov chain model in a parallel design (41).

Sequential Design

Van den Dool et al. (2008) used a sequential design in which SD and DES was combined to capture different parts of the same system (43). This approach provided emergent insights as understanding of the system was enhanced. In their study, a SD model was first built to simulate an influenza pandemic in the community. DES was then adopted to simulate the transmission dynamics of nosocomial influenza in a LTCF. As the prevalence of influenza virus in the community influences the rate at which patients, healthcare workers (HCWs) and visitors introduce the virus when they enter the LTCF, the prevalence and

the incidence of infections generated by the SD model were passed to the DES model. This hybridization improved understanding of transmission dynamics of nosocomial influenza in a LTCF by taking into consideration the impact of infection prevalence in the community on that LTCF. Wendelboe et al. (2015) reconstructed this hybrid model and validated it using the collected surveillance data for the period of 2006-2007 obtained from an active system of 76 LTCFs in New Mexico (The US) (42).

Enrichment Design

In 2011, Barnes et al. adopted an enrichment design to combine an ABM and a SD model to form a unified model. The study investigated how the interconnectivity and transfer of patients between various healthcare facilities influences the prevalence of HAIs at each facility (38). The SD model was simulated to determine the proportions of three patient states of infection (i.e., susceptible patients, persistently and transiently asymptomatic carriers) which formed a unique state for each healthcare facility. An individual facility was then modeled as an agent in a network of many healthcare facilities in the ABM. The role of the SD component was to generate the distinct characteristics of each agent and it was embedded within the ABM method. Meanwhile, the emphasis was placed on the ABM component of hybrid model as it was responsible for addressing the objectives of the study as stated above.

Integration Design

In 2013, Sadsad et al. designed a hybrid model by mixing SD and ABM into a single model in an integration design to look into MRSA transmission dynamics in a hospital at multiple-levels (40). The SD method was employed to simulate the flow of patient and HCW between different hospital wards and rooms represented as stocks. ABM was adopted to model transmission between patient agents mediated by HCW agents. During the modeling process, neither systems simulation methods were dominant, but they were inseparable.

Caudill et al. (2013 and 2017) also integrated a SD model and an ABM to form a single, unified hybrid model which respectively captured the intra-host dynamics of antibiotic resistant bacteria and inter-host dynamics of HAI spread among patients and HCWs (44, 45). The ABM component facilitated the simulation of interactions between patients and HCWs. Individual patients and HCWs were represented as agents

characterised by distinct properties and behaviors. The SD component simulated the changes in the internal pathogen population of each agent, called bacteria population vector, over time which form one of the elements driving the transmission probabilities during events of agent-interactions. This bacteria population vector of each agent defined the colonization or infection status of that agent. The statuses of agents affected the transmission of bacteria between agents. Whenever interactions between two agents occurred or patient agents received the application or dosage of a specific antibiotic, the SD component was invoked to simulate the dynamics in bacteria population vector within each agent and update its infection/colonization status. The ABM and SD component of the hybrid model were treated on an equal footing.

Interaction Design

Kardas-Sloma et al. (2013) used a previously developed ABM (i.e., NosoSim (46)) to simulate the spread of MRSA among patients and HCWs in a hypothetical ICU (39). This model was coupled with a SD model which simulated the transmission of MRSA in the community through hospital admissions and discharges. The hybrid model captured the interactive influences between hospital setting and community setting while the transmission within each setting was grounded in each method. The ABM and SD model adopted could operate independently or they could work together to enhance the understanding of the impact of overall reduction in antibiotic use upon MRSA selection in both settings.

Parallel Design

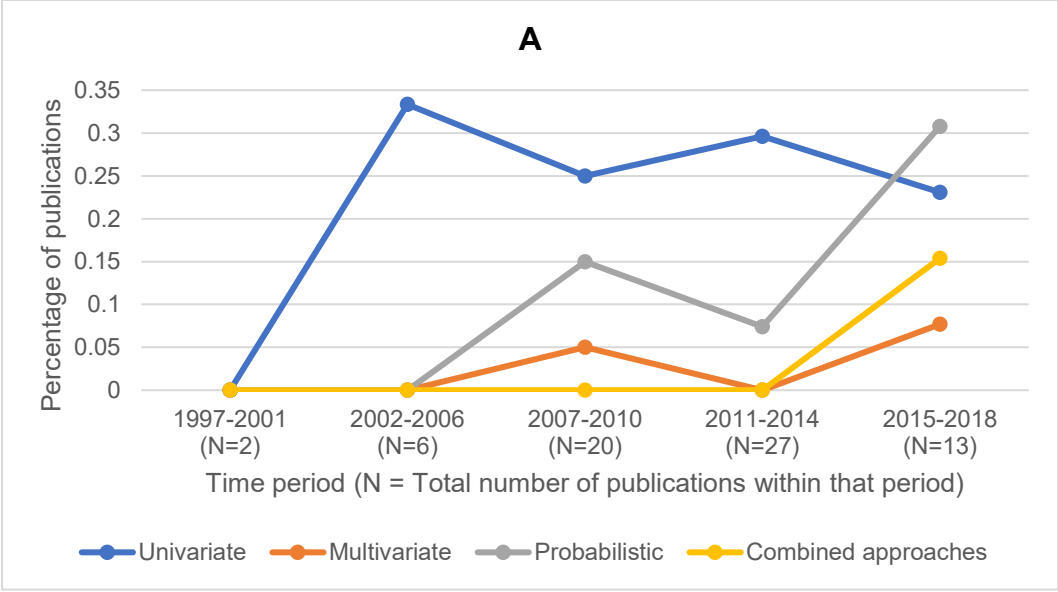
Wang et al. (2017) developed two separate HAI models using SD and a stochastic continuous time Markov chain which offered two possible representations of the transmission dynamics of MRSA in a hospital (41). The hybrid model helped obtain complementary insights of the single system and revealed plausible explanations of the system's behaviors. This was achieved by the introduction of the SD model for the transmission of MRSA in a hospital followed by a stochastic epidemic model to check the important features which had not been well illustrated in the other model. No interaction between the two models was observed.

The study of D'Agata et al. (2007) applied the same approach to model the transmission dynamics of antibiotic resistant bacteria in a hospital setting from different levels of details (37). An ABM was used to model heterogeneous patient and HCW behaviors within a typical hospital setting and simulate infection spread. A corresponding SD model represented the system at an aggregate level that provided the interpretation for the behaviors of the ABM over a large number of simulations (37).

Sequential, enrichment, interaction and integration designs of model hybridization have been useful for capturing different aspects/behaviors of the same system while a parallel design offers two possible presentations of the same system.

Sensitivity Analysis

Upon completion of building a simulation model, it is important to evaluate how sensitive/robust the model is to various sets of initial conditions that we are using (i.e., examination of the influence of varying parameter inputs on model results) because of the uncertainty of input parameter values and distributions for simulation model of HAIs (47). This process is called sensitivity analysis. Less than half of the studies included sensitivity analysis (47%, 32 studies). Of the studies that conducted a sensitivity analysis using one type of sensitivity analysis, univariate sensitivity analysis was the most common method (24%, 16 studies). Probabilistic sensitivity analysis (PSA) was the second most common method but to a significantly less extent (12%, 8 studies). PSA is generally regarded as a more rigorous method to explain uncertainty in the joint distribution of parameters (17), and is recommended in health economic evaluation guidance (48). Furthermore, two recent studies employed the combination of univariate and multivariate/probabilistic sensitivity analysis to investigate model sensitivity (49, 50). The number of studies conducting sensitivity analysis and the use of more sophisticated approaches have been increasing in recent years (Figure 2A).



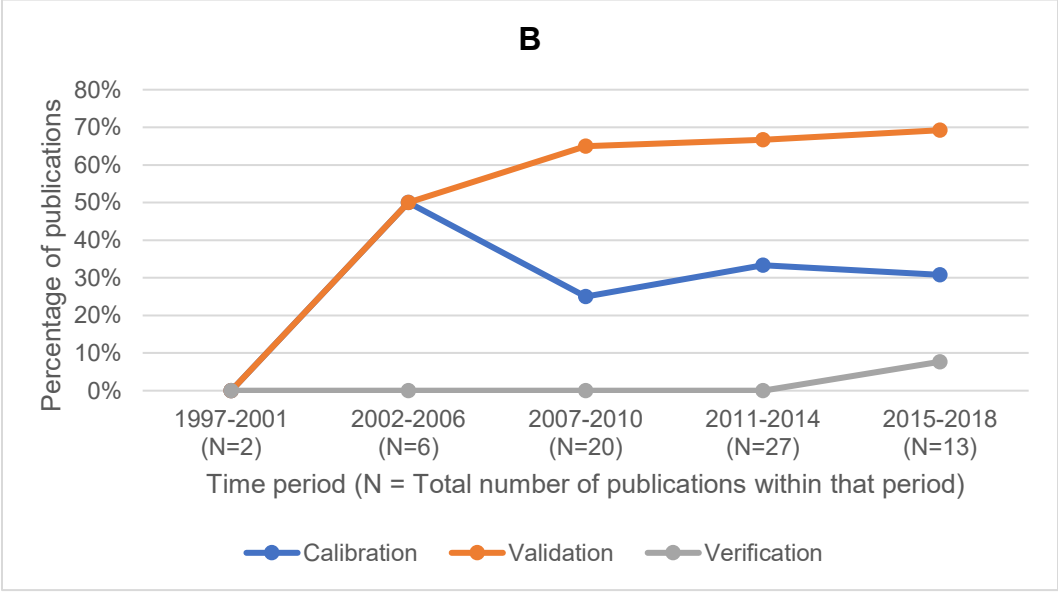


Figure 2: A/ Use of different types of sensitivity analysis over time; B/ Inclusion of calibration, validation and verification process in simulation models of healthcare-associated infections (HAIs).

Validation/Confidence Building and Verification

The usefulness of a model and its results is particularly important to many stakeholders who use the results for decision-making or who are influenced by decision-making based on models (51). The ultimate goal of validation/confidence building and verification of a simulation model is therefore to ensure the

correspondence between reality and the implemented model to the degree which satisfies the intended application or purpose of the model (47).

Extensive model validation had not been common practice in HAI simulation modeling but the percentage of publications including model validation increased until 2010 and has since remained relatively constant (Figure 2B). More than a third of the included publications did not mention any sort of validation (24 studies). Almost half of the simulation models that contained stochastic element (30 studies) were validated by using the single approach of internal validity, in which several simulations were performed to assess their stochastic variability. The lack of consistency in a model's results may cause the appropriateness of the investigated system or the strategy/policy to be questionable (51). Historical data validation, which uses a part of the collected data other than the data used for model building to test if the model behaves as the real system does (51), was found to be used as the single method of validation in 4 other studies (6%). Other validation methods were rarely used. Recent simulation models combined multiple validation methods to achieve a more thorough validation approach (37, 39, 42, 49, 50, 52-56). With respect to the different simulation methods, approximately half of SD and hybrid simulation models depicted a validation approach while a higher proportion was observed for ABM and DES models (i.e. 73% and 86% respectively). Over half of hybrid simulation models that included a validation method used combinations of validation approaches. This number occupied a third of all models using mixed approaches to validation. Only 1 out of a total of 68 studies described how verification was conducted, using good documentation of the model building process and randomly checking whether the simulated behaviors of selected agents of each type matched the intended behaviors of the conceptual model (49).

Model Parameters and Model Calibration/Model Fitting

Parameters used for the simulation models came from published studies, assumptions, and/or real-world data obtained from clinical databases, observations, surveys, or estimated directly from data. Calibration has traditionally been considered as a method to adjust unavailable or unobserved parameters, such as infection transmission rates, to achieve a good fit with the data (57). Although the proportion of models that included some form of calibration is small (31%, 21 studies), this figure increased between 1997 and 2007 and has remained stable thereafter (Figure 4). The models in this review used a number of calibration

approaches: maximum likelihood estimation (58, 59); the least square criterion (60, 61); Monte Carlo (39), Markov Chain (49), and combinations of these methods (35, 40, 50, 52, 62-64). In particular, McBryde et al. (2007) used a combination of Bayesian estimation and Markov Chain Monte Carlo for model fitting (64). Similarly, Sadsad et al. (2013) combined a scatter search algorithm and a least square criterion for model calibration (40). Other studies compared model predictions to observed epidemiological data (35, 50, 52, 62, 63) while the rest did not specify the model fitting approach.

Setting and Interaction between Settings

The simulation models of HAIs primarily depicted a single ward setting (34, 65, 66). The majority of the models included in this review simulated transmission of HAIs in an intensive care unit (ICU) setting (25%, 17 studies) or a simplified hospital setting (32%, 22 studies) of which most lacked any further ward structure (12 out of 22 studies, 55%). General wards were modeled in five studies (7%) of which three specified a particular type of ward (i.e., an out-patient long-term hemodialysis (66), a dialysis unit (67) and a vascular unit (54)). One recent study incorporated various types of hospital ward with a distinct nature into one model, including hospital wards designated as either General Care, Observation and Step-down, or characterized as surgical and medical (50). Additionally, a small number of studies (5 studies, 7%) modeled transmission dynamics of HAIs in LTCFs for pathogens such as influenza (42, 43, 68), MRSA (69) and viral nosocomial gastroenteritis (62). Pediatric health facilities were considered in merely three studies (52, 70, 71).

The majority of publications took neither transfer patterns between healthcare facilities nor transmission dynamics within healthcare settings into consideration although most ward or hospital-based simulation models included did not view the hospital as a closed system (e.g., inclusion of hospital admission and discharge rates from and into community). Recently published studies incorporated the interaction between ICUs and general wards, or between general wards within a hospital (35, 40, 49, 72, 73). Donker et al. (2010) was the first to look at the impact of different referral patterns among various categories of hospitals upon MRSA infection rates (74). A year later, two other studies also examined the interaction between settings for MRSA (38, 75). Furthermore, the studies of Lee and his colleagues published in 2013 explored

the transmission of MRSA within a setting in which multiple hospitals, LTCFs, and the community interacted with one another (76, 77).

Modes of Interaction

The majority of studies asserted that the interaction between patients mediated via HCWs is the primary cause of HAI transmission in healthcare settings (75%, 51 studies). The remaining 17 studies (25%) did not specify any types of human-human or human-environment-human interaction that had been considered in their models. In contrast, a significantly smaller proportion of models in the review simulated other types of interactions within healthcare settings. In particular, both direct contact between patients or indirect contact via a contaminated environment were modeled in 24% and 22% of the included studies respectively (16 and 15 studies), followed by direct contact between HCWs (16%, 11 studies) and visitor-patient contact (only 13%, 9 studies). Additionally, the inclusion of contact between family caregiver and HCW was a distinct characteristic of the models set up in NICU (52, 70). This type of interaction is of importance and likely to happen within pediatric healthcare settings where parents are often (if not always) involved in childcare activities.

Software

Just over half of the studies in this review specified the software on which the simulation model had been built (53%, 36 studies). Table 1 shows that C++, MATLAB, AnyLogic, and NetLogo were the most popular. Although ABM was introduced much later than SD and DES, there was a growth in the number of software available for ABM users. MATLAB, NetLogo, Anylogic and Repast were used to hybridize different kinds of simulation models, mainly for mixing SD and ABM.

Types of Healthcare Workers Modeled

Only a quarter of the publications clarified different kinds of HCW modeled. They mainly included doctors and nurses who are primarily responsible for the delivery of care in a healthcare facility, therefore having the most frequent contact with patients (24%, 17 studies). Only a small proportion of the models simulated transmission caused by HCWs other than doctors and nurses (8%, 6 studies) which included peripatetic

HCWs (46, 53), rogue HCWs (10), respiratory therapists, occupational therapists, speech therapists, physical therapists (78), admission personnel, auxiliary personnel and cleaning staff (79), and volunteers (80). Additionally, Jemenez et al. published a study in 2013 that created one of the most comprehensive social networks among patients and different types of HCWs in a simulated hospital in which individuals had their own activity schedule (78).

Interventions for HAIs Being Modeled for Effectiveness Evaluation

The main theme of simulation modeling studies in HAIs has been to evaluate the effectiveness of various IPC strategies (87%, 59 studies). The intervention strategies being investigated in the studies included in this review were: hand hygiene (39%, 23 studies), patient isolation (27%, 15 studies), screening and antibiotic stewardship (22% for each type of intervention, 13 studies), decolonization (19%, 11 studies) and HCW cohorting (17%, 10 studies). Some studies assessed the effectiveness of integrating two different IPC strategies including the effect of combining hand hygiene and decolonization for MRSA (81), isolation and screening for MRSA (35), and screening and contact isolation (82). A study published in 2015 used simulation modeling to conduct a more intensive assessment of the impact of mixing four different interventions (49). Similarly, another publication released a year later assessed the benefits of a “bundle” IPC strategy (83). Researchers have not extensively explored IPC measures such as vaccination, patient cohorting, barrier precaution, environmental disinfection and referral patterns.

Economic Evaluation

A minority of the included publications included an economic evaluation of HAIs (10 studies, 15%). A model published in 2009 first adopted DES to conduct a cost-effective analysis based on actual data from two hospitals in the US (59). This study strongly suggested the association between length of stay (LoS) and HAIs which had been ignored in previous publications (84, 85). Recently published studies paid more attention to the economic aspect of HAIs. They have estimated cost-effectiveness for different IPC strategies and investments, mainly for MRSA (59, 71-73, 86, 87) followed by CD (83, 88). Economic analyses were carried out for a single intervention (i.e., hand hygiene (59, 71), isolation (59), vaccination (70, 88), patient room design (56)), combination of two (59, 73) or three interventions (86, 87), and a

bundled strategy (83). It can be clearly seen that most studies focused on the cost-effectiveness evaluation of hand hygiene, screening and isolation. Table 2 gives a summarized description of the included studies' economic analysis for HAIs.

Table 2: Description of the studies that included economic analysis

Transferability and Generalizability

First author	Year of publication	Pathogens	Types of Model	Setting	Type of economic analysis	Interventions
Hagtvedt (59)	2009	MRSA, VRE	DES	ICU	Cost effective analysis	Hand hygiene, isolation and combination of measures
Hubben (72)	2011	MRSA	DES	Entire hospital	Cost effective analysis	Selected vs universal screening
Greer (70)	2011	Pertussis	ABM	NICU	Cost effective analysis	No vaccination vs vaccination
Robotham (86)	2011	MRSA	ABM	ICU	Cost effective analysis	Screening, isolation, decolonization and combination of measures
Gurieva (73)	2013	MRSA	DES	ICUs and general wards	Cost effective analysis	Screening, isolation and combination of measures
Nelson (83)	2016	Clostridium difficile	ABM	Entire hospital	Cost effective analysis	Bundled measure including testing, isolation, hand hygiene, contact precautions, soap and water for hand hygiene, and environmental cleaning
Robotham (87)	2016	MRSA	ABM	Entire hospital	Cost effective analysis	Options for MRSA screening for admitted patients (no screening, checklist-activated screening, and high-risk specialty-based screening), isolation, decolonization and combination of measures
Shin (56)	2017	MERS	SD	Entire hospital	Cost effective analysis	Patient room design
Stephenson (88)	2017	Clostridium difficile	SD	Entire hospital	Cost effective analysis	Vaccination strategies
Luangasanatip (71)	2018	MRSA	SD	ICUs	Cost ultility analysis	Hand hygiene

Because of economical, logistical and theoretical benefits, it is important for model users to understand how to enhance model transferability and generalizability during model development. However, as models imperfectly represent real systems and are contextually constrained during their development, care needs

to be taken when transferring and generalizing an existing model to avoid unintentional misapplication. The majority of studies included in this review did not discuss the transferability and generalizability of the developed simulation models (78%, 53 studies). Of the studies that did mention these aspects, they briefly discussed the possibility of transferring their simulation models to assess HAI transmission dynamics for different pathogens (34, 36, 40), in different healthcare settings (34, 40, 59), and to evaluate the effectiveness of different sets of interventions (36, 59). However, a methodology for model transferring or generalizing, rather than modification of parameter values, model setup and assumptions, was not clearly explained.

Benefits of Using Simulation Modeling

Only five studies mentioned the benefits of using simulation modeling in healthcare (7%). The reasoning outlined in the studies to rationalize the employment of this method included time, cost and practical and ethical considerations of experimental or observational research methods like randomized controlled trials (34, 45). Another reason was the complexity of transmission dynamics, spread and resistance of HAIs which involve numerous interdependent and dynamic interactions and cannot be completely captured by epidemiological studies (64, 89, 90). The advantages of ABM over other simulation modeling methods were also discussed in 4 papers, mainly emphasizing its capability to simulate the heterogeneity of patients and behaviors of HCWs in healthcare settings and their contact networks (36, 45, 46, 67). These studies indicated that ABM was the most appropriate for modeling an ICU where the population size is small and patient turnover is high. Neither a clearer explanation of the pros and cons of each simulation modeling nor when to combine them and what the benefits of doing so were found in the reviewed studies.

Discussion

How have Simulation Models been Used to Enhance the Understanding of HAIs and IPC?

MRSA was the predominant pathogen modeled, followed by VRE and CD to a significantly lesser degree. As MRSA accounts for high rates of morbidity and mortality, and can lead to metastatic or complicated infections like sepsis or infective endocarditis, it remains a global health issue (91). Similarly, VRE has been a significant cause of HAIs, likely affecting the most vulnerable patient groups and accounting for significant

mortality rates with prolonged LoS and therefore increased healthcare costs (92). Both of these pathogens have become the subjects of national IPC policies and the targets of national surveillance systems in a variety of HICs (92-94). Therefore, it is understandable why MRSA and VRE have been the pathogens of interest in many simulation models for HAIs.

The problems of HAIs in LMICs where the burden is significantly higher than HICs are rarely addressed in the literature and particularly in simulation modeling studies. The prevalence of HAIs in LMICs is at least double the prevalence in Europe (9). Additionally, the incidence of HAIs acquired in ICUs in LMICs triples the incidence in the US (95). However, our review found that only a minority of simulation models for HAIs in LMICs were developed.

ICUs have remained the subject setting of several simulation models as they are one of the most dynamic and complex areas in a hospital. Simulation models for HAIs have also become more complex in terms of the settings being modeled. Earlier studies generally modeled a single ward (usually an ICU) or a simplified hospital lacking of any further ward structure while more recent studies were likely to incorporate different types of wards (ICUs and general wards), as well as consider the transmission across health facilities (e.g., mainly between hospitals), and the community. Future studies could investigate interactions with LTCFs, other types of healthcare facilities, and the community to provide a more realistic estimate of HAI incidence and prevalence, and the effectiveness of IPC policies. Pediatric settings were rarely considered although pediatric patients have higher rates of viral lower respiratory tract infections and bloodstream infections than adults, especially those younger than 2 years of age and those demanding care in NICUs and pediatric ICUs (96).

As the most popular transmission routes of infections in healthcare settings are via the transiently colonized hands of HCWs and/or contaminated medical equipment and the environment, modeling interactions between patient and HCW has dominated this field of research, followed by the environmental reservoir for transmission although to a much lesser extent. Simulation modeling studies have hardly considered direct HCW-to-HCW contact or interactions between visitors/caregivers and patients. Visitors/family caregivers can play a very important role in infection transmission in a health facility, especially in settings such as pediatric or geriatric health facilities where patients often need extra care. In many cultures including Asian

468 countries and LMICs, having visitors and caregivers on a regular basis is common practice and sometimes
469 encouraged due to a considerable shortage of staff and a need to reduce medical costs to patients (56).
470 As visitors and caregivers are also more mobile than patients, they are both highly susceptible to contracting
471 infections and potentially able to transmit pathogens to various locations inside and outside as the hospital
472 (78).

473 *When to Use Which Simulation Modeling Method?*

474 The application of three types of simulation models to investigate HAIs has greatly changed over time. SD
475 is suitable for investigating the long-term behavior of the system containing large patient populations which
476 are considered to be homogenous and therefore aggregated into compartments (97). Thus, it is useful for
477 macro-level modeling to reflect long-term consequences and discover long-term solutions that may provide
478 effective aids in policy decision making at a high-level. Although SD has long been used to analyze HAI
479 dissemination in hospitals and IPC policies, it could not address the spatial detail and microstructure of a
480 healthcare facility, the complexity and heterogeneity of contact networks within a healthcare setting and the
481 stochasticity of interactions within such networks (79).

482 By contrast, ABM has been found to be significantly helpful in overcoming the limitations of SD which may
483 explain the increasing use to model HAIs in recent years. It is easier and thus preferable for modeling the
484 heterogeneity of a small population like an ICU rather than a large population setting (98). Healthcare
485 settings in general and ICUs, in particular, are spatially intricate environments where complex interactions
486 between specific sets of individuals are a key driver of transmission. Not every primary physician,
487 consultant, and nurse see every patient, leading to a highly heterogeneous social and contact network (36).
488 Diagnostic uncertainty (i.e., whether an individual is infected is not always known) also complicates the
489 transmission of HAIs. This accentuates the importance of impacts of stochastic interactions and chance
490 events upon the transmission and spread of HAIs. ABM can also help understand the influence of different
491 patient referring and transferring patterns among healthcare facilities within a network due to variations in
492 their geographical locations, policies, services provided and variations in individuals' decision. A limitation
493 of ABM is the requirement of reliable and detailed data for model building and validation which are not
494 always readily available (61). Higher levels of behavioral detail produced by ABM causes greater

computational intensity, and difficulty in performing model parameterization and extensive uncertainty analyses which are essential for reliable predictions. As ABM and hybrid models become increasingly popular, the adoption of more sophisticated methods and mixed methods for sensitivity analysis, calibration and validation were more frequently observed in more recently published studies.

Similar to ABM, DES allows incorporation of detailed patient attributes and is well-suited for modeling the procedure of activities that patients need to progress through (99). However, unlike ABM, DES does not consider social contacts and interaction among individuals, and therefore, transmission of infections needs to be simulated indirectly in a DES model (100). DES cannot model individual-level behaviors such as learning, adapting and autonomous decision-making as ABM does. Nor can it capture feedbacks in a system as SD does. It is, therefore, less satisfactory for simulating transmission of pathogens, possibly accounting for the less frequent application of this simulation modeling method in HAIs in comparison with the use of SD and ABM.

The adoption of hybrid simulation models has become increasingly common. As all three simulation modeling methods have different benefits, limitations, strengths, and weaknesses, mixing methods potentially overcome some of the drawbacks faced by using a single approach and/or provide more plausible explanations of a problem which a single method on its own could not handle. For example, SD is useful in providing a holistic view of the feedback dynamics of HAI transmission in a complex healthcare system but cannot take account of the heterogeneity of individual patients and HCWs, and the stochasticity resulting from their behaviors and interactions which are the distinct features of ABM. As healthcare systems are highly complex, dynamic and interconnected, HAIs and other problems in the context of healthcare gained from different simulation modeling methods may benefit from the complementary view gained from using multiple simulation modeling methods together. However, a clear framework and philosophical foundation for hybridization have not yet been established in any of the reviewed publications.

Few studies included in this review explicitly explain why they choose one method over the others to answer their research questions. Therefore, the rationale underlying the use of different simulation methods in HAIs is still not clear. The choice of simulation method should be problem-driven and depend on the research objectives and the availability of data. Future modeling studies should be encouraged to include explicit

explanation for the selection of a specific simulation method. This would provide insights for researchers and modelers in this field with respect to the different uses for each simulation methodology. Furthermore, a full framework for choosing a simulation method should be broached in future research.

Implication

The review provides an overview of the development and application of systems simulation modeling in HAIs from which gaps of research in this field can be identified. Firstly, the transmission patterns of HAIs in LMICs require further studies as they are likely to be dramatically different from the ones in HICs due to many factors such as poor infrastructure, insufficient environmental hygiene conditions, different staff cohorting, shortage of HCWs, HCWs' knowledge and compliance to IPC measures, overcrowded healthcare facilities, absence of comprehensive IPC guidelines and policies, lack of procedure, and different antibiotic prescribing and referral patterns. Secondly, pediatric hospitals and other types of healthcare setting like LTCFs, as well as interactions between settings were not extensively investigated. Furthermore, understanding of patient sharing and referring networks among healthcare facilities driven by operational and financial alliances needs to be improved. Thirdly, the number of studies adopting hybrid simulation models are still limited, possibly because of the unavailability of clear guidelines and frameworks for hybrid model development. As it is argued that most, if not all, real-world problems tackled with simulation modeling cannot be solved by SD, DES or ABM alone but require a combination of two or all of them, a hybrid model resulting from this combination expectedly offers different perspectives of a problem and generate more insights which will provide better understanding and greater support for decision-making (101). The use of simulation modeling for economic analysis of different IPC measures and strategies has increased but is still relatively scarce. The application of this method to evaluate the cost-effectiveness of various IPC strategies is promising in a sense that it can appropriately guide and prioritize the allocation of limited resources and funds. Additionally, understanding of other kinds of interactions in the healthcare setting apart from interactions between doctors/nurses and patients is insufficient. Lastly, the evaluation of clinical and cost effectiveness was only conducted for a number of commonly used interventions like hand hygiene, isolation, and screening, further investigation on other IPC measures and a combination of different strategies is imperative to determine best practice in various healthcare settings. Models can also

549 be developed to simulate coordination and collaboration among health facilities to assess the impact of a
550 regional IPC program.

551 **Conclusion**

552 The review aims to consolidate and update the development and application of systems simulation
553 modeling in studying HAIs. It can help guide further development of simulation models, especially hybrid
554 models, to target gaps in knowledge in this field of research. As a summary, the results of this review
555 indicate that the complexity of simulation models for HAIs, in terms of level of details of healthcare settings
556 and interactions being modeled and methodological designs, significantly increased over time but the
557 context predominately remained focused on the transmission dynamics of MRSA in hospitals in HICs, rather
558 than in other types of healthcare settings such as LTCFs or in LMICs. Furthermore, the overview of existing
559 simulation models in HAIs can facilitate and direct researchers to useful areas for further research such as
560 transmission of HAIs in healthcare settings other than hospitals and across different types of settings.
561 Further development and application of hybrid simulation models could help to secure further insights into
562 HAIs.

563 **List of Abbreviations**

564	HAIs	Healthcare Associated Infections
565	IPC	Infection Prevention and Control
566	HICs	High-Income Countries
567	LMICs	Low- and Middle-Income Countries
568	ABM	Agent-Based Model
569	SD	System Dynamics
570	DES	Discrete Event Simulation
571	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis

LTCFs	Long-Term Care Facilities
MRSA	Methicillin-Resistant *Staphylococcus Aureus*
VRE	Vancomycin-Resistant *Enterococci*
NICU	Neonatal Intensive Care Unit
CD	*Clostridium Difficile*
HCWs	Healthcare Workers
LoS	Length of Stay
PSA	Probabilistic Sensitivity Analysis
ICU	Intensive Care Unit.

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable as this review does not contains any individual person's data in any form.

Availability of data and material:

Further data and material are available upon request to the corresponding author.

Competing interests:

The authors declare that they have no competing interests.

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LN contributed to the methodological design of the review, underwent data extraction and analysis, and wrote the first draft of the manuscript. IM and SH contributed to the methodological design of the review. All authors edited and approved the final manuscript.

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Appendix A

Table A1: Characteristics of the reviewed studies

Reference	Country of Research	Setting	Type of Simulation Model	Cost Effectiveness Analysis	Pathogen	Intervention	Type of HCWs included	Inclusion of Direct HCW-HCW Contact	Inclusion of Direct Patient-Patient Contact	Inclusion of Patient-Visitor Contact	Inclusion of HCW-Patient Contact	Inclusion of Transmission via Contaminated Environment	Inclusion of Interactions Between Settings
Sebille et al. (1997) (34)	Not specified	ICU	SD	No	MRSA	Hand hygiene, antibiotic stewardship, isolation	N/A	Yes	No	No	Yes	Yes	No
Lipsitck et al. (2000) (65)	Not specified	ICU	SD	No	Not specified	Hand hygiene, barrier precautions	N/A	No	Yes	No	Yes	No	No
D'Agata et al. (2002) (66)	The US	General ward	SD	No	VRE	HCW cohorting, hand hygiene	N/A	No	No	No	Yes	No	No
Cooper et al. (2004) (58)	UK and Denmark	Hospital*	SD	No	MRSA	Isolation	N/A	No	No	No	Yes	No	No
D'Agata et al. (2005) (89)	The US	Hospital*	SD	No	VRE	Hand hygiene, antibiotic stewardship, HCW cohorting	N/A	No	No	No	Yes	No	No
Hotchkiss et al. (2005) (36)	Not specified	ICU	ABM	No	MRSA, VRE	Isolation, patient cohorting, HCW cohorting	Nurses, primary physicians, and consultant physicians	No	No	No	Yes	No	No
Webb et al. (2005) (102)	Not specified	Hospital*	SD	No	Not specified	N/A	N/A	No	No	No	Yes	Yes	No
Bootsma et al. (2006) (35)	Netherlands	Hospital	DES	No	MRSA	Isolation, screening and combined interventions	N/A	No	No	No	Yes	No	Yes (ICUs and general wards)
Basu et al. (2007) (60)	South Africa	General ward	SD	No	Multi-drug resistant tuberculosis	Isolation, HIV treatment, air ventilation, facial mask	N/A	No	No	No	Yes	No	No
Boldin et al. (2007) (103)	Not specified	ICU	SD	No	Pseudomonas Aeruginosa, enteric Gram-negative bacteria, MRSA and enterococci	Barrier precautions (improved hygiene, gloves, gowns), antibiotic prophylaxis	N/A	No	Yes	No	Yes	No	No
D'Agata et al. (2007) (37)	Not specified	Hospital*	Hybrid (SD + ABM)	No	Anti-biotic resistant nosocomial pathogens	Antibiotic stewardship	N/A	No	No	No	Yes	No	No
Hotchkiss et al. (2007) (67)	The US	Dialysis unit	ABM	No	Not specified	Environment disinfection, patient cohorting	N/A	No	No	No	Yes	Yes	No
McBryde et al. (2007) (64)	Australia	ICU	SD	No	MRSA	Hand hygiene, HCW cohorting, decolonization, patient cohorting	N/A	No	No	No	Yes	No	No
Nuno et al. (2008) (68)	Not specified	LTCF	SD	No	Influenza	Non-pharmaceutical interventions	N/A	No	No	No	No	No	No

Ueno et al. (2008) (104)	Japan	Hospital*	SD	No	Not specified	Isolation, HCW cohorting, vaccination	Nurses and medical doctors	Yes	Yes	No	Yes	No	No
van den Dool et al. (2008) (43)	Netherlands	LTCF	Hybrid (SD + DES)	No	Influenza	Vaccination	N/A	Yes	Yes	Yes	Yes	No	Yes (LTCF and community)
Wolkewitz et al. (2008) (105)	Germany	General ward	SD	No	VRE	Hand hygiene, antibiotic stewardship, screening, patient cohorting, environmental cleaning	N/A	No	No	No	Yes	Yes	No
D'Agata et al. (2009) (97)	The USA	Hospital*	SD	No	HA-MRSA, CA-MRSA	Hand hygiene, screening, decolonization	N/A	No	No	No	Yes	No	No
Greer et al. (2009) (52)	Canada	ICU	ABM	No	Pertussis	Vaccination strategies	N/A	Yes	No	Yes	Yes	No	No
Hagtvedt et al. (2009) (59)	The USA	ICU	DES	Yes	MRSA, VRE	Hand hygiene, isolation	Doctors and nurses	No	No	Yes	Yes	No	No
Temime et al. (2009) (53)	Not specified	ICU	ABM	No	Staphyloccocus aureus, Enteroccoci, MRSA, VRE	Hand hygiene	Nurses, physicians and Peripatetic HCWs	Yes	No	No	Yes	No	No
Vanderpas et al. (2009) (62)	Belgium	LTCF	SD	No	Viral nosocomial gastroenteritis	N/A	Nurses and medical staffs	No	No	Yes	Yes	Yes	No
Barnes et al. (2010) (10)	Not specified	Hospital*	ABM	No	MRSA	Hand hygiene, isolation, screening, decolonization, HCW cohorting,	Physicians, nurses, rogue HCWs	No	No	Yes	Yes	No	No
D'Agata et al. (2010) (106)	The US	ICU and general ward	SD	No	HA-MRSA and CA-MRSAa	Hand hygiene, decolonization	N/A	No	No	No	Yes	No	No
Donker et al. (2010) (74)	The Netherlands	Hospital network	ABM	No	MRSA	Referral patterns	N/A	No	No	No	No	No	Yes (Different categories of hospitals)
Meng et al. (2010) (107)	UK	Hospital ward	ABM	No	MRSA	Isolation, decolonisation	Doctors, nurses	No	Yes	No	Yes	Yes	No
Temime et al. (2010) (46)	Not specified	ICU	ABM	No	Not specified	Hand hygiene	Nurses, physicians and Peripatetic HCWs	No	No	No	Yes	No	No
Webb et al. (2010) (81)	Not specified	Hospital	SD	No	HA-MRSA, CA-MRSA	Hand hygiene, decolonization and combination of these interventions	N/A	No	No	No	Yes	No	No
Barnes et al. (2011) (38)	The US	Hospital and LTCF	Hybrid (SD + ABM)	No	MRSA	Screening, decolonization	N/A	No	No	No	No	No	Yes (Hospitals and LTCFs)
Chow et al. (2011) (90)	Not specified	Hospital*	SD	No	Antibiotic-resistant pathogens (not specified)	Antibiotic stewardship	N/A	No	No	No	No	No	No
Greer et al. (2011) (70)	Canada	ICU	ABM	Yes	Pertussis	Vaccination strategies	N/A	Yes	No	Yes	Yes	No	No
Hubben et al. (2011) (72)	Netherlands	Hospital	DES	Yes	MRSA	Screening, isolation	N/A	No	No	No	Yes	No	Yes (ICUs and general wards)

Kardas-Sloma et al. (2011) (61)	EU countries and The US	ICU and general ward	ABM	No	MRSA	Antibiotic stewardship	N/A	No	No	No	No	No	No
Kouyos et al. (2011) (75)	The US and Ireland	A setting in which several hospitals interact with the community	SD	No	Not specified (Dataset from Ireland included MRSA)	Antibiotic stewardship	N/A	No	Yes	No	No	Yes	Yes
Lanzas et al. (2011) (63)	The US	Hospital ward	SD	No	Clostridium difficile	N/A	N/A	No	No	No	No	No	No
Lee et al. (2011) (108)	The US	Hospitals (Excluding pediaetric hospitals)	ABM	No	MRSA	N/A	N/A	No	No	No	No	No	Yes (Within a hospital, between hospitals and between hospitals and community)
Milazzo et al. (2011) (54)	UK	Vascular unit	ABM	No	MRSA	Hand hygiene, HCW cohorting	N/A	No	No	No	Yes	No	No
Robotham et al. (2011) (86)	UK	ICU	ABM	Yes	MRSA	screening, isolation, and decolonisation	N/A	No	No	No	No	No	No
Wang et al. (2011) (80)	China	Hospital*	SD	No	MRSA	Hand hygiene	HCWs in general and volunteers	No	No	No	Yes	Yes	No
Barnes et al. (2012) (109)	Not specified	ICU	ABM	No	Antibiotic resistant bacteria (eg. MRSA) or airborne diseases (eg. Influenza or tuberculosis)	HCW cohort	Nurses, physicians	Yes	Yes	No	Yes	No	No
Chamchod et al. (2012) (69)	Not specified	LTCF	SD	No	MRSA	Hand hygiene, screening, decolonization and isolation	N/A	No	Yes	No	Yes	No	No
Gurieva et al. (2012) (110)	Netherlands	Hospital	DES	No	MRSA	Decolonization, isolation	N/A	No	No	No	Yes	No	No
Lee et al. (2012) (82)	The US	Hospitals (Excluding pediaetric hospitals)	ABM	No	MRSA	Active surveillance, contact isolation (wearing gloves and gowns), combintion of interventions	N/A	No	No	No	No	No	Yes
Caudill et al. (2013) (44)	Not specified	Hospital ward	Hybrid (SD + ABM)	No	Staphylococcus aureus and Pseudomonas aeruginosa, MRSA	Antibiotic treatment	N/A	Yes	Yes	No	Yes	No	No
Ferrer et al. (2013) (111)	An EU country	ICU	ABM	No	Unspecified pathogens	N/A	Physicians and nurses	No	No	No	Yes	No	No
Gurieva et al. (2013) (73)	Netherlands	Hospital	DES	Yes	MRSA	Screening and isolation	N/A	No	No	No	Yes	No	Yes (ICUs and general wards)

Jimenez et al. (2013) (78)	The US	A floor of the hospital	ABM	No	Clostridium difficile	Antibiotic stewardship	Physicians, nurses, respiratory therapists, occupational therapists, speech therapists, physical therapists	Yes	Yes	No	Yes	No	No
Kardas-Sloma et al. (2013) (39)	France	ICU	Hybrid (SD + ABM)	No	MRSA	Antibiotic stewardship	N/A	No	No	No	Yes	No	No
Lee et al. (2013a) (55)	The US	Hospitals (Excluding pediaetric hospitals)	ABM	No	VRE	N/A	N/A	No	No	No	No	No	Yes
Lee et al. (2013b) (77)	The US	Hospitals (Excluding pediaetric hospitals) and LTCFs	ABM	No	MRSA	N/A	N/A	No	No	No	No	No	Yes
Lee et al. (2013c) (76)	The US	Hospitals (Excluding pediaetric hospitals) and LTCFs	ABM	No	MRSA	Contact precautions	N/A	No	No	No	No	No	Yes
Rubin et al. (2013) (112)	Not specified	Hospital	ABM	No	Clostridium difficile	isolation, hand hygiene, barrier precautions (gloves), enviromental disinfection	Physicians, nurses	No	No	No	Yes	Yes	No
Sadsad et al. (2013) (40)	Australia	Hospital	Hybrid (SD + ABM)	No	MRSA	HCW cohorting, screening, isolation, hand hygiene, ward staffing level	Nurses	No	No	No	Yes	No	Yes (Wards and rooms)
Ciccolini et al. (2014) (113)	UK and The Netherlands	Multiple hospitals	SD	No	MRSA, VRE	screening	N/A	No	No	No	Yes	No	Yes (Between hospitals)
Ferrer et al. (2014) (114)	An EU country	ICU	ABM	No	MRSA, VRE, influenza	HCW cohorting	Physicians and nurses	No	No	No	Yes	No	No
Codella et al. (2015) (49)	The US	Hospital	ABM	No	Clostridium difficile	Antibiotic, hand-hygiene, isolation, environment disinfection and mixed strategies	N/A	No	Yes	Yes	Yes	Yes	Yes (HCWs can travel to different wards when not servicing patients)
Jaramillo et al. (2015) (79)	Spain	Emergency department	ABM	No	MRSA	Hand hygiene, isolation material	Doctors, triage nurse, clinical nurses, admission personnel, auxiliary personnel and cleaning staffs	No	No	No	Yes	Yes	No
Wendelboe et al. (2015) (42)	Mexico	LTCF	Hybrid (SD + DES)	No	Influenza	Vaccination	N/A	Yes	Yes	Yes	Yes	No	Yes (LTCF and community)

Nelson et al. (2016) (83)	The US	Hospital*	ABM	Yes	Clostridium difficile	Bundle including testing, isolation, hand hygiene, contact precautions, soap and water for hand hygiene, and environmental cleaning		No	No	No	Yes	Yes	No
Robotham et al. (2016) (87)	UK	Hospital*	ABM	Yes	MRSA	Screening	N/A	No	No	No	No	No	
Caudill et al. (2017) (45)	Not specified	Hospital ward	Hybrid (SD + ABM)	No	Staphylococcus aureus	N/A	N/A	Yes	Yes	No	Yes	No	No
Lei et al. (2017) (115)	China	Two hypothetical patient rooms	SD	No	MRSA	Environment disinfection	N/A	No	No	No	Yes	Yes	No
Perez et al. (2017) (116)	The USA	ICU	DES	No	Not specified (Catheter-associated urinary tract infections)	N/A	Nurses	No	No	No	No	No	No
Shenoy et al. (2017) (50)	The US	Hospital ward	DES	No	MRSA/VRE	N/A	N/A	No	Yes (Roommates)	No	No	No	No
Shin et al. (2017) (56)	South Korea	Hospital	SD	Yes	MERS	Operational interventions	N/A	No	Yes	Yes	Yes	Yes	No
Stephenson et al. (2017) (88)	The USA	Hospital*	SD	Yes	Clostridium difficile	Vaccination	N/A	No	No	No	No	No	No
Wang et al. (2017) (41)	China	Hospital*	Hybrid (SD + stochastic continuous time Markov chain)	No	MRSA	Hand hygiene, environment disinfection	N/A	No	No	No	Yes	Yes	No
Luangasanatip et al. (2018) (71)	Thailand	ICU	SD	Yes	MRSA-BSI	Hand hygiene	N/A	No	Yes	No	Yes	No	No
Hospital*: A hospital that lack any further ward structure N/A: Information is not available													

911