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Health analytics and disease modeling for better understanding of healthcare-associated infections

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Abstract:

Healthcare-associated infections (HAIs) are a growing challenge and a major cause of health concern worldwide. It is difficult to understand precisely the dynamics of spread of hospital-acquired infections owing to the usual involvement of different populations, risk factors, environments, and pathogens. Mathematical and computational models have proved to be useful tools in providing realistic representations of HAI dynamics and the means of evaluating interventions to minimize the risk of HAIs.

Keywords:

Agent-based modeling, compartmental modeling, hospital-acquired infections, nosocomial infections

Healthcare-associated infections (HAIs), also known as "hospital-acquired infections" or "nosocomial infections," refer to infections that may occur in a patient following his/her hospital admission, infections that were neither present nor incubating at the time of admission. Infections acquired in the health-care setting but manifesting postdischarge, along with occupational infections among facility staff, fall under the umbrella of HAIs.[1]

Commonly occurring HAIs include *Clostridium difficile* infections, central line-associated bloodstream infections, pneumonia, methicillin-resistant *Staphylococcus aureus* (MRSA) infections, surgical site infections, urinary tract infections, and vancomycin-resistant enterococci (VRE) infections, among others.[1] Factors contributing to HAIs and related costs include, but are not limited to, use of invasive devices, surgical procedures, selection pressure from excessive antibiotic use, contaminated air-conditioning systems, physical layout of the facility, staffing (nurse to patient ratio), use of immunosuppressive agents, underlying conditions among patients, and their interactions.

The World Health Organization estimates that HAIs occur among 7%–12% of hospitalized patients globally and more than 1.4 million individuals globally suffer from complications of HAIs.[1,2] Estimated burden of HAIs is disproportionate for developing countries. It is estimated that there is a prevalence of 4.5% in the U.S (9.3 infections/1000 patient-days) while in Europe, HAI prevalence is 7.1% (19 infections/1000 patient-days). The International Nosocomial Infection Control Consortium (INICC) conducted a cohort study in 55 intensive care units of 8 developing countries, including India, and found an overall HAI prevalence rate of 14.7% (22.5 infections/1000 patient-days). Later studies in India have revealed varying prevalence estimates from as low as 4.4% to as high as 83%.[3] Nevertheless, HAIs act as major causes of death, disability, emotional suffering, and financial burden among hospitalized patients.[4-7]

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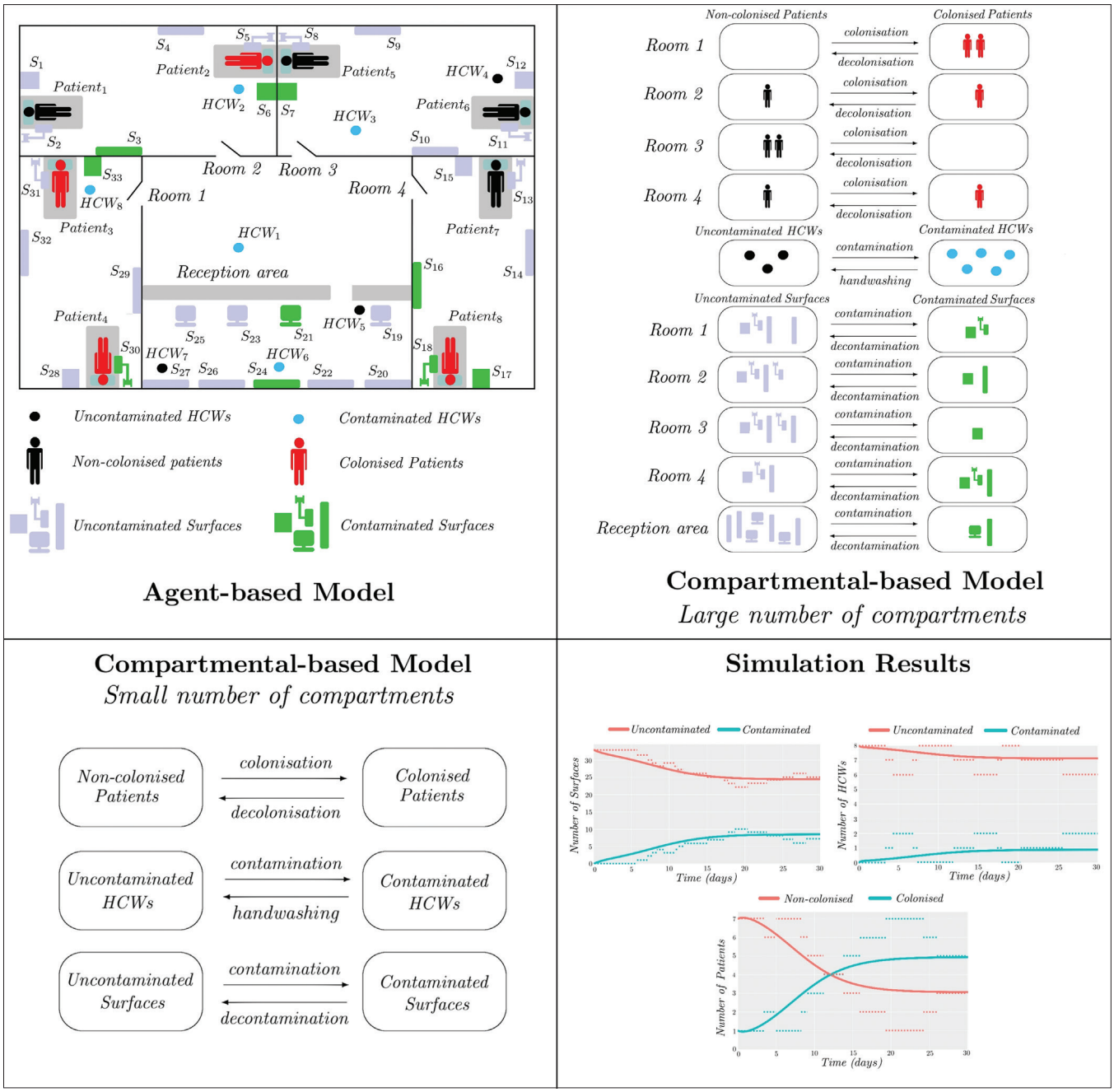

Figure 1: Mathematical and computational models for healthcare-associated infections. A model in which patients can be colonized or noncolonized by a given species of bacteria, surfaces in the hospital ward can be contaminated or uncontaminated by the bacteria, and health-care workers can have their hands contaminated or uncontaminated. Transmission occurs between patients, health-care workers, and surfaces over time. Top-left: In an agent-based model, the state of each individual is tracked over time, and the spatial movement, the interactions between agents and the duration of these interactions, as well as the transmission of the nosocomial pathogen can be simulated. Top-right: In a compartmental-based model, individuals are split into groups, where individuals in the same group are considered to behave equally. Heterogeneities among agents (e.g., the location of each agent in different rooms) can be incorporated by increasing the number of compartments. The transmission of the nosocomial pathogen among agents is represented by the movement of agents across different compartments through time, which occurs (stochastically or deterministically) according to some rates (i.e., model parameters). Bottom-left: Compartmental-based models with smaller number of compartments assume wide homogeneities among individuals, but depend on less parameters and generally require less data to be calibrated. Bottom-right: Deterministic models (solid curves) lead to the same predictions given identical initial conditions. Stochastic simulations (dotted curves) lead to different results each time one simulates the model, due to randomness

In India, accurate estimates of HAI burden are limited due to the absence of reliable and routine standardized surveillance data. Benchmarking by INICC enables development of standards and surveillance for HAIs in developing countries, thereby leading to identification of strategies to prevent and/or mitigate infections in health-care facilities. Barriers to system-wide policies for effective minimization of HAI risk include lack of mandatory hospital accreditation, lack of HAI surveillance systems, excessive antibiotic use, limitations

in sterilization and disinfection practices, and limited access to microbiology services.

Many hospitals have begun infection control committees with targeted interventions such as the use of infection prevention and control bundles to prevent surgical site infections and infections from inserted devices.[8] While efforts to strengthen hospital surveillance and build capacity are underway, systematic surveillance including data generation and rapid analytics need to be adequately addressed. In the mathematical and computational sciences, models have been developed to identify predictive pathways to understand emergence and spread of pathogens among hospitalized patients or compare efficacy of different interventions across health-care facilities. In this paper, we discuss such mathematical and computational models and their usefulness in providing realistic representations of HAI dynamics.

Models of Healthcare-Associated Infection

Mathematical and computational models of spread of HAI usually depend on a number of parameters that directly affect and determine disease dynamics, for example, admission and discharge rate of patients in a given ward, antibiotic prescription rates, average patient length of stay in the ward, or contact rates between the health-care workers (HCWs) and patients. By calibrating these models using hospital infection data, they could become realistic representations of the infection dynamics occurring in the modeled health-care facilities. Furthermore, one can study and measure the impact of different control interventions[9,10] or assess the role played by each potential route of transmission[11] (e.g., endogenous and exogenous routes, airborne spread, environmental contamination, HCW-patient direct contact transmission, etc.) in the dynamics of a nosocomial outbreak.

Models can be analyzed from either deterministic or stochastic points of view. In a deterministic approach, identical initial conditions (say, a given nosocomial pathogen is introduced in a hospital setting by the admission of a colonized patient) lead to the same final outcomes (i.e., if the nosocomial outbreak is simulated twice in a deterministic model, the same number of patients will become colonized during these two outbreaks). In a stochastic representation, identical initial conditions may lead to different outcomes resulting from random sequences of events.

Often, deterministic approaches are chosen for modeling dynamics of infection spread in large and widely homogeneous populations. Their main advantage is that they are more tractable from a computational perspective than their stochastic counterparts, which is why the early mathematical models on hospital-acquired infections were mostly deterministic.[12] However, stochastic models were adopted soon due to the highly heterogeneous nature of the populations usually involved in nosocomial outbreaks, in which probabilistic events can have a significant impact on the infection spread dynamics.[13]

Common classes of stochastic models include Agent-based models (ABM) and Compartmental-based models (CBM). In an ABM, the model keeps track of the state (e.g., a patient colonized or noncolonized or a surface contaminated or uncontaminated by a given bacterium) of each agent (e.g., patients, HCWs, or surfaces) during the course of a nosocomial outbreak.[14,15] By computationally simulating the interactions between agents over time (e.g., a colonized patient contacting an HCW, touching a surface, being admitted or discharged), one can realistically simulate the transmission of the nosocomial pathogen among different agents or possibly the recovery of individuals (e.g., decolonization of a patient due to antibiotics).[13] ABMs allow for complex and precise representations of reality, in which highly heterogeneous populations and interactions can be modeled,[16] despite requiring significant computational resources for the model analysis[17] and calibration.[18,19]

A CBM is constructed by grouping individuals in compartments according to their disease state and the type of individual under consideration where all individuals in the same compartment are considered to behave identically regarding the infection dynamics. For instance, a given compartment may be formed by all colonized patients in the hospital ward or by all the HCWs with their hands contaminated by a given bacteria. CBMs are computationally and analytically more tractable and require less amount of data in order to be calibrated as they usually depend on a smaller number of parameters compared to ABMs. However, they assume wide homogeneity among individuals which might not be realistic in certain clinical situations.[20,21] While heterogeneities among individuals can be incorporated by increasing the number of compartments, the tradeoff between the number of compartments, the computational requirements, and the availability of data must be considered [Figure 1].

Bayesian approaches may be used to find plausible values of the model parameters so that the model predictions compare well with these data.[22] Once the model can realistically represent the infection dynamics for a given hospital ward and nosocomial pathogen, one can carry out sensitivity analysis of the model, in which parameters are varied (to represent, for example, interventions based on infection control strategies or the implementation of novel surveillance policies) and the impact on the

dynamics is studied. This can lead to quantitative measures of the relative efficacy of these interventions, which may be validated using clinical data.[23]

In the Medical Research Council of the United Kingdom funded project, "Mathematical modeling of the emergence and spread of antibiotic-resistant bacteria in healthcare settings: a stochastic approach (MMARB)," new mathematical models are being developed, together with methodologies for analyzing and simulating these models, in order to better understand nosocomial infection dynamics. A number of recently published works within this project[17,20,24-28] have focused on a wide range of factors (antibiotic resistance, environmental contamination, airborne spread, strain competition, genetic heterogeneities, surveillance and screening policies, or infection control strategies), which are usually involved in the spread of hospital-acquired infections.

The Road Ahead

This section will focus on infection control strategies and surveillance policies, assessing the role played by environmental contamination, and other factors and current challenges regarding HAIs.

One of the primary objectives when developing mathematical models in this area is to quantify the efficacy of the different control strategies commonly implemented for controlling nosocomial outbreaks. For example, models have focused on the efficacy of the following interventions: improving hand-hygiene compliance levels among HCWs,[29] environmental cleaning,[30] active colonization screening among patients and HCWs,[31] isolation of colonized individuals and patient cohorting,[13] or antibiotic prescription.[32] Recent studies[24] within the MMARB project focus on modeling such interventions through a unified framework, which allows assessment of the role played by the different transmission routes during a nosocomial outbreak (e.g., environmental contamination or HCW-patient transmission) and thus, to measure the relative efficacies of the modeled control strategies.

A number of recent studies have highlighted the role played by environmental contamination in the spread of some nosocomial pathogens since it has been observed that pathogens such as MRSA and VRE are able to survive on dry surfaces for weeks[33] and may be transmitted through a large number of surface-to-hand and hand-to-surface contacts. This has led to modeling of the amount of transmission that occurs during each surface-hand contact,[34] the deposition of bacteria from the air on surfaces[35] to incorporate contaminated/uncontaminated surfaces as agents,[30] and to incorporate into these models realistic hand-surface contact patterns carried out by patients and HCWs, as those actually observed in hospital settings in reality.[35]

Ventilation and airflow dynamics within a hospital ward are important factors affecting the spread of some nosocomial pathogens such as influenza, *Norovirus*, or tuberculosis.[17,24] A number of studies have incorporated the dynamic airflow within individual health-care facilities into their models to study the airborne spread of such nosocomial pathogens.[36-38] In this area, complex computational fluid dynamics models can be proposed, which focus on modeling the movement of air across different rooms and areas over time and the spread of airborne pathogen-laden particles or bio-aerosols.[38]

These models can be used to simulate how bio-aerosol concentration of a given pathogen varies in space and time, how aerial dispersion and inhalation of these pathogens occurs, and how strategies related to hospital ventilation and outbreak management can be implemented for infection control. In a recent collaboration within the MMARB and the HECOIRA[39] projects, authors have focused on how to incorporate the aerial dispersion of a nosocomial pathogen into a mathematical model for the spread of this pathogen within a hospital ward, taking into account the ventilation of the health-care facility under analysis and the spatial location of the patients in this facility.

The transmission of a nosocomial pathogen among patients and HCWs in a hospital ward depends, among others, on two factors: the interactions between HCWs and patients, where specific HCWs treat only some patients in the ward (e.g., patient cohorting), and the spatial configuration of the hospital ward. For example, infection transmission between patients in the same room might be more likely than transmission between patients at different rooms. While some studies have tried to incorporate these spatial and contact network information into their mathematical models,[13] challenges remain on how such models may be calibrated[18] or to develop effective methodologies needed for handling model complexity in these situations.[17,24]

Only a few studies have looked at the dynamics of competition between bacterial strains in hospital settings, for example, antibiotic-resistant versus antibiotic susceptible or hospital-acquired versus community-acquired strains. It is worth mentioning the seminal work by Lipsitch,[32] in which authors consider a simple mathematical model to study the competition dynamics between an antibiotic-resistant strain and an antibiotic-sensitive strain in a hospital ward, and the effect of different antibiotic prescription policies in this situation.

Studies have also looked at the competition between hospital-acquired and community-acquired strains,[40] or the impact of the introduction of community-acquired strains on hospital settings,[41] but further research is needed in this area. In particular, within the MMARB project and when focusing on a number of antibiotic prescription policies, a new methodology for carrying out sensitivity analysis of the model (i.e., to study the impact that each parameter has on the final nosocomial outbreak outcome) was published recently.[25]

Moreover, the mathematical modeling of nosocomial infections has overwhelmingly focused on hospital settings, whereas healthcare-related facilities other than hospitals (such as nursing homes or clinical microbiology laboratories) have been usually neglected. Developing new models for better understanding the nosocomial infection spread in these settings is a current challenge (that is also being addressed within the MMARB project[26]). Further, a variety of events occur within a host (such as the immune response or the emergence of antibiotic resistance) that can clearly have an impact on the nosocomial infection, and novel methodologies for analyzing this infection dynamics occurring across scales are needed. Here, it is worth mentioning a recent study which links infection processes across different scales, at the cellular, within-host, and population levels, to model the dynamics of the spread of the bacteria *Francisella tularensis* within a microbiology laboratory.[26]

Finally, more collaborative efforts in the collection of hospital infection data through an interdisciplinary network of disease modelers, microbiologists, and clinicians are required. The models must be calibrated with data capturing the conditions that are specific to a nosocomial outbreak, including patients, pathogens, and hospital wards. The development of technological innovations such as microbiome analysis, proximity sensors, or individual location monitoring systems can generate detailed spatial and temporal data regarding individual behaviors and agent-to-agent interactions in hospital settings. Together, they allow integrated data-driven models to be designed, which may lead to predictions and actionable insights required to improve the handling of the emergence and spread of hospital-acquired infections.[42]

Discussion

HAIs present a complex and costly problem given the involvement of different populations, risk factors, environments, and pathogens. Due to the high mortality associated with HAIs, prevention and control remain the first-line strategies to address HAIs. There is growing recognition around the world, including in many developing countries, for the need of policy and guidance documents to address the rising challenge of HAIs. In India, the Indian Council of Medical Research released in 2016 guidelines on infection prevention and control.[43] Addressing laboratory facilities and testing along with other systems-related factors is critical.

Interventions in the public sphere including Swacch Bharat mission (Clean India) and Kayakalp (clean hospitals) may go on to demonstrate effectiveness in curbing infection spread. Cooperation between various health-care entities and across sectors (public, private, etc.) is important and must entail detailed surveillance along with strengthening institutional capacity and building networks for rapid dissemination of information. The National Accreditation Board of Hospitals and National Health Mission in India have paved the way to sustain health-care surveillance and incorporated infection control programs as a routine part of clinical care.

It is important to create a data-driven culture with a strong commitment to improve health-care outcomes. Monitoring the system for effectiveness and compliance is essential in order to develop practice standards that are consistent with established benchmarks. The use of analytics and modeling to track and evaluate the interventions and different programs is perhaps the next step in improving the HAI outcomes in India and other developing countries.

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Conflicts of interest

There are no conflicts of interest.

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