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Modeling transmission of pathogens in healthcare settings

Anna Stachel^{a,*}, Lindsay T. Keegan^{b,*}, Seth Blumberg^{c,d} CDC MInD Healthcare Program

^aDepartment of Infection Prevention and Control, New York University Langone Health, New York, New York

^bDivision of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, Utah

^cFrancis I. Proctor Foundation

^dDivision of Hospital Medicine, Department of Medicine, University of California San Francisco, San Francisco, California, USA

Abstract

Purpose of review—Mathematical, statistical, and computational models provide insight into the transmission mechanisms and optimal control of healthcare-associated infections. To contextualize recent findings, we offer a summative review of recent literature focused on modeling transmission of pathogens in healthcare settings.

Recent findings—The COVID-19 pandemic has led to a dramatic shift in the modeling landscape as the healthcare community has raced to characterize the transmission dynamics of SARS-CoV-2 and develop effective interventions. Inequities in COVID-19 outcomes have inspired new efforts to quantify how structural bias impacts both health outcomes and model parameterization. Meanwhile, developments in the modeling of methicillin-resistant *Staphylococcus aureus*, *Clostridioides difficile*, and other nosocomial infections continue to advance. Machine learning continues to be applied in novel ways, and genomic data is being increasingly incorporated into modeling efforts.

Summary—As the type and amount of data continues to grow, mathematical, statistical, and computational modeling will play an increasing role in healthcare epidemiology. Gaps remain in producing models that are generalizable to a variety of time periods, geographic locations, and populations. However, with effective communication of findings and interdisciplinary collaboration, opportunities for implementing models for clinical decision-making and public health decision-making are bound to increase.

Keywords

computational model; healthcare-associated infection; machine learning; mathematical model; nosocomial infection

Correspondence to Seth Blumberg, University of California, San Francisco, CA, USA. Seth.Blumberg@ucsf.edu.

*Anna Stachel and Lindsay T. Keegan contributed equally to this article.

Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Approximately 4% of all hospitalized patients develop healthcare-associated infections (HAIs) within the United States [1]. Although significant progress has been made in reducing HAIs, an important complication of HAIs is infections due to multidrug-resistant organisms (MDRO). In the United States, antimicrobial resistant infections have resulted in over 35 000 deaths annually, with an estimated cost of \$4.6 billion [2,3■].

The acquisition and transmission of HAIs is a complex process that depends on microbiology, clinical factors, human behavior, and health system infrastructure. The interplay of each of these factors has resulted in challenges in measuring and understanding the key components of HAI epidemiology [4]. In light of these challenges, mathematical, statistical, and computational models play a key role in quantifying the drivers of HAI epidemiology, as well as identifying effective interventions [5]. The ongoing COVID-19 pandemic has further highlighted the importance of transmission in hospitals. Here, we review key studies published in 2020 and early 2021, provide an overall perspective on the utility of modeling HAIs, highlight critical gaps in the literature, and suggest research areas that require additional study.

Mathematical, statistical, and computational models are tools for delineating, interpreting, and understanding patterns in real-world data. Mathematical models incorporate a mechanistic understanding of disease transmission, with parsimonious quantification of pathogen spread and the impact of control interventions. Statistical models, including many machine learning techniques, are agnostic to underlying mechanistic properties. These types of models are typically designed to identify correlations between observed variables that can be exploited for risk assessment or forecasting. Computational models, which include microsimulations and agent-based models, permit increased complexity of modeling assumptions but risk the inclusion of many variables whose values can be challenging to infer from data. Computational models can be used to produce forecasts, perform counterfactual simulations of how disease dynamics may have been altered by specific control interventions, or analyze how sensitive specific outcomes are to modeling assumptions. Often a model has a combination of features and cannot be neatly classified as being mathematical, statistical, or computational. In this review, we focus on how modeling has been used to improve the field of healthcare epidemiology, rather than delving into the intricacies of methodological development.

KEY PATHOGENS

SARS-CoV-2

The elephant in the 2020–2021 hospital room has been COVID-19. Over the last year, SARS-CoV-2, the virus responsible for COVID-19 rose from relative obscurity to over 120 million detected cases worldwide (as of 16 March 2021) [6,7]. The meteoric rise in cases has been paralleled by a similar rise in modeling research. The early focus of modeling centered around community transmission, healthcare utilization needs, and projections of interventions designed to maintain health system integrity [8–12]. In addition, forecast and

simulation studies sought to explore the risk of nosocomial transmission of SARS-CoV-2 among healthcare personnel and patients [13].

As the pandemic evolved, significant attention has been paid to modeling nosocomial transmission of SARS-CoV-2 in long-term care facilities (LTCFs). Early in the pandemic, LTCFs proved to be particularly high-risk settings due to high concentrations of individuals with high-risk comorbidities and the congregate living arrangement. Consequently, a number of modeling studies sought to understand LTCF bed needs, testing requirements for preventing transmission, and optimal vaccine deployment strategies [14,15–18].

Methicillin-resistant *Staphylococcus aureus*

The CDC estimated that in 2019 there were over 320 000 cases of methicillin-resistant *Staphylococcus aureus* (MRSA) in the United States resulting in over 10 000 deaths [3]. MRSA colonization is associated with susceptibility to invasive infection, highlighting the benefit of identifying who might benefit from decolonization regimens. One study aimed to make screening more cost-effective by developing a clinical prediction rule for identifying patients at high risk of being colonized with MRSA [19]. The model showed that a negative predictive value of 99.4% can be maintained when just 25.4% of patients are screened. In another study, the possibility of MRSA superspreading events within and between healthcare facilities was shown in an analysis of an extensive contact network of patients, emphasizing the impact and importance of screening on admission [20].

Models also addressed the effectiveness of interventions for preventing MRSA transmission. In a large-scale study of 108 Veterans Affairs acute care hospitals, Khader *et al.* [21] found contact precautions for MRSA patients reduced transmission by 47%. Furthermore, genomic surveillance of MRSA is likely to be cost-effective based on the reduction of MRSA acquisitions in the year following an admission [22].

Extended spectrum beta-lactamase-producing *Enterobacteriaceae* and other multidrug-resistant organisms

MDROs are a frequent contributor to HAI [1]. The CDC estimated that for 2019 there were over 197 000 extended spectrum beta-lactamase *Enterobacteriaceae* infections resulting in over 9000 deaths [3]. Modeling of epidemiological data for multidrug-resistant *Klebsiella* in Europe suggested that nosocomial transmission and hospital-based antibiotic consumption were the major drivers of transmission at a national level [23]. Thus improvements in infection prevention and antimicrobial stewardship may impact the emergence and spread of MDRO in both the hospital and community.

An important avenue of investigation focuses on how antibiotic resistance emerges as a consequence of clinical care. It has been suggested that the evolutionary rate for developing antimicrobial resistance is growing more quickly due to a nonlinear coupling between increased antibiotic use and the emergence of antibiotic resistant strains. However, it is unclear whether the observation of increased rapidity of antimicrobial resistance is simply a consequence of increased surveillance [24]. Models have also explored the potential impact of bystander exposure in which nonpathogenic bacteria in a patient develop drug resistance after they are exposed to antibiotics that are targeted for an invasive pathogen.

In one analysis, up to 48% of bystander antibiotic exposures might be avoidable in the outpatient setting [25]. However, more studies are needed to quantify the relationship between bystander exposure and clinically meaningful antibiotic resistance [26].

Clostridioides difficile

Clostridioides difficile infection (CDI) is a frequent complication of medical treatment. In 2017, nearly 224 000 people in the United States required hospital care for CDI and at least 12 000 people died [3■]. Models of CDI have been used to assess the amount of transmission occurring within the hospital system, and thus offer perspective on the effectiveness of prevention and control efforts. For example, a combination of electronic health record and sequencing data lead to an estimate that 21% of CDI cases were acquired from another patient due to overlapping stays or via spores left behind on discharge [27■■]. This study also demonstrated strain dependence in both the transmissibility and durability of spores.

It has long been recognized that there is significant heterogeneity in transmission of CDI. This may be due to host, pathogen, or environmental factors. Models can be used to tease apart the causes of heterogeneity. For example, a recent modeling study using *C. difficile* surveillance data found that different wards in the same hospital can exhibit different nosocomial transmission dynamics [28].

TRANSMISSION CONTROL AND DISEASE PREVENTION

Infection prevention

A challenge in healthcare epidemiology is quantifying the benefit of specific control interventions such as the implementation of contact precautions. As more detailed data are made increasingly available, studies are beginning to place bounds on the impact of contact precautions and how it varies by organisms [21■,29].

An intriguing complexity of infectious disease dynamics is the inter-relationship between transmission pathways for multiple pathogens. For example, a model of the MRSA surveillance and prevention strategy in the Veterans Affairs system quantified how the impact of interventions designed to reduce the spread of MRSA may have also prevented a substantial number of infections from other organisms [30].

Building upon success in the control of nosocomial influenza transmission through targeted vaccination campaigns, there has been increased interest in vaccination as a tool for combatting other HAIs [31,32]. In advance of a promising CDI vaccine, Toth *et al.* quantified the indirect effects of a potential vaccine. This study suggested that between three and 16 CDI cases per 1000 vaccinated patients could be averted, including one to five cases among unvaccinated individuals [31].

Another approach to HAI prevention is decolonization of organisms that can precipitate invasive infection. The cost-effectiveness of new antibiotics, antiseptics, and other technologies that decolonize carriers of drug-resistant organisms appears markedly enhanced when the impact on community transmission is incorporated [33]. This poses an intriguing

preventive strategy but would require reassessment of approval mechanisms for novel decolonization technologies.

Antimicrobial stewardship

Studies continue to show the benefit of antimicrobial stewardship programs in reducing HAI. For example, by curtailing nonspecific use of antibiotics, cases of CDI have been lowered by over 30% in some hospitals [34]. Several studies characterized the importance of coordinating antimicrobial stewardship programs among inpatient, outpatient and LTCF for reducing CDI and MDRO burden [35–37]. Other studies show the potential value of prediction algorithms for identifying patients on empiric antibiotics who have a very low risk of having a bloodstream infection [38].

The development of antimicrobial resistance is enhanced by antibiotic selection pressure; thus, there is increased interest in elucidating the relationship between the clinical use of antibiotics and emergence of antimicrobial resistant strains [39]. A recent model by Hansen *et al.* [40] suggested a minimalist strategy to exploit competitive suppression of selective strains over resistant strains so that chronic control of both invasive infection and resistance can be achieved.

TRENDS IN MODELS AND METHODOLOGIES

The promise of genomics

The widespread availability of genomic data coupled with the increase in computational power has resulted in rapid development of methods that have significantly improved our ability to identify transmission links among patients. For example, a study by Eyre *et al.* [27] developed a novel approach for integrating pathogen genomic data into an agent-based model for CDI transmission in a hospital setting. This methodology permitted inference of patient-to-patient transmission links while accounting for genetic recombination, readmission and additional routes of transmission such as persistent environmental contamination.

The COVID-19 pandemic has led to additional methodologic improvements for incorporating genomic data into epidemiological models. A study by Meredith *et al.* [41] used genomic data and epidemiological analyses of patients in a hospital to identify clusters of SARS-CoV-2 transmission. The results helped clinical, infection control, and hospital management teams to improve interventions and patient safety. Similarly, a study by Rockett *et al.* [42] coupled genomic analysis with an agent-based model to identify the ratio of local versus imported acquisition of SARS-CoV-2 in Australia.

Applications of machine learning technologies

Several studies have shown the use of machine learning to identify patients at high risk of acquiring various types of HAI. For example, one study developed a model to predict the probability of a urinary tract infection caused by a MDRO [43]. Another study predicted patients at high risk for central line-associated bloodstream infections (CLABSI) [44]. The

risk of surgical site infections has also been explored [45]. The diversity in recent studies illustrates the broad applicability of machine learning methodologies.

CRITICAL GAPS AND FUTURE CHALLENGES

Inequities and inequalities in healthcare modeling

The COVID-19 pandemic has highlighted disparities in outcomes across socioeconomic status, residential neighborhood, race, and ethnicity [46,47]. Models can help characterize structural factors that lead to inequity. Epidemiologic and population-level modeling studies have explored the extent to which inequities arise from variability in hospital care, heterogeneous exposure in the workplace, higher rates of comorbidities in certain subpopulations, and geographic localization of intergenerational households [48–50]. While studies have begun to explore disparities, additional modeling studies are needed to translate these descriptive findings into actionable interventions such as improving access to healthcare or addressing mistrust that some communities have of the medical profession [51].

Predictive models for HAI should continue to explore the specific impact of demographic factors such as sex and race. Although a number of studies include demographic variables in the model building process, causal dependencies can be challenging to illicit. For example, a study identified black race as a predictor for CLABSI risk, but it was unclear whether this relationship was due to self-identified race serving as a proxy for socioeconomic factors [44]. In addition, the effects of implicit bias on prediction models deserve more attention. In particular, implicit biases may affect the selection of training data and thus bias predictions.

Transitioning from theory to implementation

Despite this era of seemingly endless computational resources, challenges of model generalizability, and applicability abound [52,53]. A common problem identified in models focused on risk estimation is that they are invariably trained for a specific time and location. However, inevitable changes in epidemiology, treatments, or patient demographics can necessitate retraining or rewriting a model.

Internal validation of models requires a balance between accurate parameterization and overfitting. Thus, there are trade-offs between a time-invariant model that includes minimal site-specific information and a complex microsimulation model for which data might be lacking to support the specific assumptions. One approach for addressing this challenge may be to use machine learning algorithms to parameterize mechanistic models tailored to our best scientific understanding of the spread of disease [5].

Beyond internal validation, barriers to implementation of algorithms include assurance of quality standards that are transferable across locations. For example, resistance patterns to antimicrobials in urinary tract infections can generally differ from region-to-region, and even from ward-to-ward within a hospital [43]. Encouragingly, many studies use separate hospital cohorts for external validation. However, careful consideration of the external validation is needed before broad application to a new health system. For example, training and external validation of a model using data in a single country may not translate well to

other countries. Similarly, results based on data from urban areas may not apply to more rural areas. Additional studies are needed to evaluate how technologies such as propensity score matching can help evaluate the generalizability and safe clinical application of models beyond the time periods and populations in which internal and external validation was conducted [54].

Finally, a critical gap exists between statistical validation of models and the implementation of these advances for clinical or public health decision-making. All too often well developed models are not deployed to address the problems they target; rather they languish in academic journals collecting dust. To transition models from a theoretical concept to practical implementation requires communication among modelers, healthcare workers, healthcare administrators, and public health officials [55,56]. In particular, the rapid, high stakes collaborative effort that brought modelers, hospital administrators, and public health officials together to manage the COVID-19 pandemic has shown that greater emphasis on the deployment process is needed to efficiently and effectively address future outbreaks [57,58■].

CONCLUSION

Recent studies continue to demonstrate how modeling research can be applied to understand the mechanisms driving disease transmission in healthcare settings. The COVID-19 pandemic has expanded the scope and urgency of these investigations, particularly with regard to characterizing inequities in disease outcome. Meanwhile, the overall impact of modeling research for prevention and control of HAIs will depend on further advancements in implementation research.

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KEY POINTS

- Mathematical modeling can help disentangle the complex interplay of factors that impact the transmission of pathogens in healthcare settings.
- Commonly modeled pathogens in 2020 were SARS-CoV-2, methicillin-resistant *S. aureus* and *C. difficile*.
- Innovative methodologies are taking advantage of the surge in genomics data and the development of machine learning technologies.
- Future challenges for modeling research include addressing inequities in healthcare and transforming theoretical results into meaningful implementation.