SHEA WHITE PAPER

Research Methods in Healthcare Epidemiology and Antimicrobial Stewardship—Mathematical Modeling

Sean L. Barnes, PhD;[1] Parastu Kasaie, PhD;[2] Deverick J. Anderson, MD, MPH;[3] Michael Rubin, MD, PhD[4]

Mathematical modeling is a valuable methodology used to study healthcare epidemiology and antimicrobial stewardship, particularly when more traditional study approaches are infeasible, unethical, costly, or time consuming. We focus on 2 of the most common types of mathematical modeling, namely compartmental modeling and agent-based modeling, which provide important advantages—such as shorter developmental timelines and opportunities for extensive experimentation—over observational and experimental approaches. We summarize these advantages and disadvantages via specific examples and highlight recent advances in the methodology. A checklist is provided to serve as a guideline in the development of mathematical models in healthcare epidemiology and antimicrobial stewardship.

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Mathematical models are abstract representations of real-world systems and can serve as tools to inform clinical decision-making. They can support a variety of efforts in healthcare epidemiology and antibiotic stewardship (HE&AS), including guiding data collection and empirical analysis, testing explanatory hypotheses about mechanisms driving observed real-world patterns, and informing policy as well as intervention design and evaluation. Mathematical models are classified on the basis of several criteria, including whether they are used to model system behavior that is static or dynamic, stochastic or deterministic, and discrete or continuous. In this review, we provide an overview of 2 of the more common types of mathematical models used to understand and describe infectious diseases: compartmental models and agent-based (AB) simulation models. More detailed information about mathematical modeling (as applied to HE&AS) is available in several key references.[1–10]

ADVANTAGES AND DISADVANTAGES

Mathematical modeling provides several advantages over observational and experimental approaches (Table 1).[11–13] For instance, models can be used to gain insight when experimenting with the real system is too difficult, time consuming, expensive, or unethical. In addition, mathematical models can help to evaluate the external validity of traditional studies and explore scenarios beyond observed settings. By contrast, translating insight generated from modeling analyses into practice is difficult because practitioners often rely on more traditional experimental methods (eg, randomized controlled trials) to inform decision-making. Modeling teams also require a distinct and typically multidisciplinary set of individuals to be productive; in addition to clinicians, mathematicians, and programmers, modeling groups often include statisticians, epidemiologists, and data analysts, among others, which can raise the barrier to entry for research in this domain.

Compartmental Models

Compartmental modeling is a widely used methodology for simulating the behavior of complex systems, typically characterized by dynamic, tightly coupled, and nonlinear behavior that is difficult to characterize using other methods.[14] The most common form of a compartmental model leverages a system of coupled ordinary differential equations to model the dynamics of one or more quantities of interest over time. As applied to healthcare epidemiology, compartmental models are most often used to model how proportions of susceptible, infected, and recovered individuals evolve over time in a healthcare or community setting (Figure 1).

Compartmental models are often specified via a set of analytical equations that are computationally inexpensive to simulate and therefore are easily scaled to different-sized systems. These equations can be used to explicitly derive

Affiliations: 1. Department of Decision, Operations & Information Technologies, Robert H. Smith School of Business, University of Maryland, College Park, Maryland; 2. Department of Health, Behavior and Society, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland; 3. Department of Medicine, Duke University School of Medicine, Durham, North Carolina; 4. Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah.

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TABLE 1. Advantages, Disadvantages, and Potential Pitfalls of Using Mathematical Modeling in Healthcare Epidemiology and Antimicrobial Stewardship Research

Model type	Advantages	Notes
Any	Virtual environment that facilitates extensive experimentation and sensitivity analysis, including under various current conditions and future states	Useful when experiments in practice are not possible, too costly, or time consuming
	Relatively short developmental timeline and rapid experimentation	
	Leverage advancing computational power	
Compartmental	Computationally inexpensive	
	Easily replicable	
	Easily scalable	
	Facilitates analytical results and insights	eg, Basic reproduction number, R_0, as a relative measure of epidemic growth rate over time
AB	Detailed modeling of individual characteristics and behavior (heterogeneity)	Increases flexibility for individual-level dynamics
	Intuitive conceptual models	
	Detailed modeling of interventions at the individual and population levels	
Model type	**Disadvantages**	**Notes**
Any	Obtaining buy-in from practitioners	
	Translating insight into practice	
Compartmental	Simplifies model dynamics for analytic tractability	Often assume mass action principle
	Limited ability to capture heterogeneity	Individuals typically treated as identical
	Limited accuracy for smaller systems	Particularly for deterministic models
AB	Computationally expensive	Parallelization helps to mitigate computational costs
	Difficult to scale	
	Difficult to replicate	
	Implementation, calibration, validation, and experimentation driven by complexity	
	Lack of data at the individual level	
	Limited curriculum for potential modelers	User-friendly platforms are emerging[11–13]
Model type	**Potential pitfalls**	**Tips and solutions**
Any	Inappropriate model complexity	Work with clinical practitioners to gauge complexity and define outcomes
	Lack of proper validation and calibration	Compare output with data from observational, experimental studies Use multilevel statistical validation
	Lack of generalizability due to model parameters informed by single sites	Use parameters informed by multiple sites when data is available
	Sensitivity analysis extends beyond scope of reality	Focus sensitivity analysis on realistic range of parameter values, ideally informed by data and literature
Compartmental	Oversimplification of model dynamics	Limit scope to larger systems for which aggregated dynamics are more appropriate
AB	Overly detailed and complex models	Reference problem statement to limit "scope creep"

NOTE. AB, agent-based.

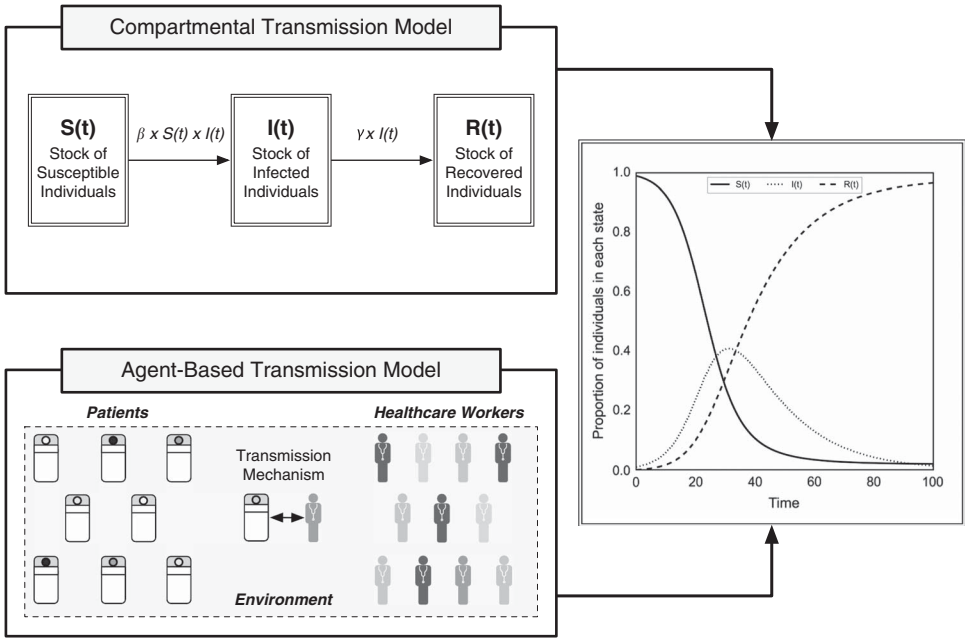

FIGURE 1. Key feature summary of compartmental and agent-based transmission models. Compartmental modeling is a top-down approach that models the evolution of stocks of susceptible, infected, and recovered individuals over time and flows of individuals between the compartments. Note that β is the transmission rate and γ is the recovery rate. Agent-based modeling is a bottom-up approach that explicitly simulates interactions between potentially heterogeneous agents (eg, patients, healthcare workers) in a defined environment, which serves as the mechanism for transmission. Individual agent states are aggregated to monitor stocks of susceptible, infected, and recovered individuals over time. Both modeling approaches can generate the dynamics shown in the figure to the right; however, stochastic variations are not shown, which are present in some systems dynamics models and most agent-based models.

important relationships between model parameters. The most notable result from this type of analysis is the basic reproduction number (R_0), which represents the expected number of secondary cases per primary case in an entirely susceptible population. These types of results can provide significant insight into system dynamics because the results are generalizable across all parameter values and do not have to be explicitly observed or simulated.

By contrast, these models often oversimplify transmission dynamics in favor of analytic tractability (ie, the ability to solve and simulate the system of equations) and are somewhat limited in their ability to capture heterogeneity (ie, individual characteristics and behavior). For example, compartmental models often assume the principle of mass action—through which all individuals in the population are equally likely to interact with each other.[15] Also, most experimentation with compartmental models is conducted in the form of sensitivity analysis, through which model parameters are varied and the effects on primary outcomes are observed. Although useful, this approach can sometimes have limited impact if the experimentation does not reflect realistic scenarios.

AB Models

AB modeling provides a more explicit representation for studying complex, dynamic systems[16–19] and serves as a virtual laboratory for exploring new approaches to infection control. AB models consist of a set of "agents" that encapsulate the behaviors of various entities that constitute the system of interest. Agents can interact with each other and/or the environment on the basis of a set of simple rules that lead to a series of population-level patterns or outcomes (Figure 1), many of which may be unexpected (a concept known as *emergence*). In doing so, these models can be used to estimate the risks of disease and the effects of interventions at the individual level.

AB models offer significant flexibility for modeling dynamics at the individual level that will generate behaviors at the population level. In the context of infectious disease modeling, these dynamics include the definition of contact networks, mobility patterns, and characteristics relevant to disease progression and treatment outcomes at the individual level that govern disease transmission at the population level. Moreover, the multilevel nature of such models enables explicit definition of various interventions at the patient, facility, and community levels (eg, contesting TB contact-tracing with an active-case finding campaign[20]) and provides a powerful experimental platform to study the system's behavior and predict future trends. Unlike many (deterministic) compartmental models, AB models explicitly capture system uncertainty via the direct application of random variables, thus providing a more realistic framework for representing

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stochastic (ie, random) behaviors and estimating risks associated with potential interventions.

The realism generated by these models, however, is offset by the additional complexity in development and analysis, as well as computational demands for experimentation (particularly for large-scale models). Traditional programming languages used to develop AB models demand considerable computer programming expertise and can be time consuming. A standard curriculum for teaching AB simulation rarely exists.[21] Furthermore, the complex structure and parameter-rich nature of AB models pose several challenges for calibration, validation, and sensitivity analysis.[22]

PITFALLS AND TIPS

Some pitfalls in mathematical modeling can be limited through use of best practices (Tables 1 and 2). First, model detail should match the complexity of the problem being studied. Compartmental models often oversimplify model dynamics, which can lead to models that do not capture the behavior of the system sufficiently well. By contrast, AB models are often overly complex relative to the problem being modeled. Excessively detailed models can lead to unreasonable data and computational demands that may limit the scope of analysis and, in turn, serve as a barrier to translating findings into practice. The best practice of modeling is seeking the simplest approach that enables answering the question of interest, or in other words, "make things as simple as possible but no simpler" (attributed to Albert Einstein). Along these lines, modelers and practitioners must work closely together to ensure that model complexity is appropriate given the problem under study.

Another key pitfall of mathematical modeling involves validation and calibration of the model, because these processes improve the model's ability to produce results similar to the actual system. Many modeling studies are limited in this regard, performing only cursory (and often subjective) checks that 1 or 2 model outputs are similar to observed measures of the same. Calibration is especially challenging for large-scale AB models that employ many parameters, and these models often require a multilevel statistical validation focused on both individual- and population-level outcomes. Modeling human behavior and the interactions between agents is a difficult challenge; thus, efforts to validate modeled behavior with social theories are often neglected. Finally, many models are often calibrated to reproduce the behavior of a single site, rather than to approximate more representative behavior across multiple sites. We recommend that future modeling studies dedicate more robust efforts to this process and execute proper hypothesis testing to demonstrate that model outputs are representative of observed performance measures.

MATHEMATICAL MODELING IN HEALTHCARE EPIDEMIOLOGY AND ANTIBIOTIC STEWARDSHIP—REVIEW OF SPECIFIC EXAMPLES

Many applications of mathematical modeling in HE&AS research consist of 2 primary objectives:

1. To simulate the dynamics of patient-to-patient transmission of resistant or susceptible organisms in a healthcare or community setting
2. To evaluate the effect of model-based parameters or interventions on transmission of, and infection with, clinically relevant organisms

TABLE 2. Checklist of Key Considerations When Developing a Mathematical Model for Healthcare Epidemiology and Antimicrobial Stewardship Research

1. *What steps should be taken in order to get started with a mathematical modeling study?* Establish a joint collaboration between modelers and practitioners to define the problem statement and develop the conceptual model.
2. *How does one define an appropriate scope?* Model complexity and structure should be relevant to the problem under study.
3. *What software should be used to develop a mathematical model?* Selected model implementation software should be commensurate with skill, experience, model complexity, and requirements for analysis and documentation. There are a substantial number of programming languages, open-source modeling tools, and commercial off-the-shelf software packages that can be used to develop mathematical models, for both compartmental[59,60] and AB models.[61–63]
4. *How does one determine what values to assign to model parameters?* Model parameters should be informed by observational data (ideally from multiple sites) and/or published literature when available.
5. *What steps should be taken to ensure that the model outputs are accurate?* Model teams should perform extensive verification to ensure the model is implemented correctly and model parameters should be calibrated and (empirically) validated to match primary outputs (eg, acquisition rates).
6. *What type of analysis should be performed on the output from mathematical models?* Analyze results in a manner appropriate for the model and approachable to the intended audience, and perform appropriate sensitivity analysis of results to modeling assumptions and parameters.
7. *How should the results of the study be reported?* Documentation of model design, analysis, and implications should be commensurate with target publication outlet. In addition, model files (and associated parameter values) should be made available for public evaluation when possible.

NOTE. AB, agent-based.

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Deterministic compartmental models—for which model dynamics are entirely predictable for a given set of model equations and initial conditions—have been adapted to many applications in HE&AS research since their inception.[23–28] D'Agata and colleagues[26] improved on earlier transmission models of the type using proportions of susceptible, infected, and recovered individuals by including additional compartments for patients on the basis of whether they were receiving antibiotics, which can affect the likelihood of acquisition or transmission. However, the inclusion of these additional compartments—although more realistic—also led to complex model equations with many unknown parameters.

A major limitation of many of the aforementioned studies is that they do not account for the variability often observed in the prevalence of colonized and/or infected patients and healthcare workers over time. More recent compartmental models have incorporated stochastic dynamics, which better account for this behavior, particularly in smaller systems such as intensive care units.[29–35] For example, Bootsma and colleagues[35] developed such a model across 3 hospitals to evaluate several infection control interventions with many parameters informed by a large, tertiary care medical center in the Netherlands. This was one of the first such compartmental models to attempt to capture the effect of superspreaders and patients with high risk of acquisition, 2 characteristics more naturally suited to AB modeling.

AB models have been applied to the study of disease spread in a variety of settings, ranging from specific care units[18,36] to emergency departments,[37] hospitals,[38–40] nursing homes,[41,42] and communities.[43] AB models enable better incorporation of population heterogeneity with regard to population demographic characteristics, contact networks, and mobility patterns.[6] For example, Macal et al[43] modeled community-based MRSA transmission in a synthetic population based on Chicago, Illinois, which included distinct representations of individual demographic characteristics (eg, age, gender, race) and activity patterns informed by national survey data. This model produced an accurate estimate of community-associated MRSA incident rates from 2000 through 2010, but also required a broad set of assumptions, extensive data from disjoint sources, and extensive development and calibration.

Some studies actually employ both methods and compare them directly.[15,27] For example, Rahmandad and Sterman[15] construct susceptible-exposed-infected-recovered models using compartmental and AB approaches over a variety of contact network structures. They highlight many of the aforementioned advantages and disadvantages of each approach but also stress the importance of finding a balance between the 2 paradigms, stating that results can be indistinguishable for larger and more homogenous populations. Sensitivity analysis is also critical, but extensive analysis in this dimension is difficult for computationally intense AB models.

Many compartmental and AB transmission models are accompanied by systematic analysis of one or more model-based parameters or potential infection control interventions. Hand hygiene compliance is by far the most studied intervention[18,25,26,28–30,32,33,38,44–46]; however, many studies have also used mathematical models to investigate the potential benefits of cohorting,[24,29,32,33,38,45] active surveillance and diagnostic testing (ie, to identify colonized but asymptomatic patients),[26,29,30,34,35,38,47] contact precautions and isolation,[26,31,35,38] decolonization,[38,48,49] and environmental cleaning.[39,44] In addition, authors have used these models to investigate the impact of several key model-based parameters, such as admission prevalence, unit/ward size, pathogen transmissibility, contact rates, and length of stay.[27,30,33,44]

On the larger scale, few studies have analyzed interfacility or regional effects of transmission.[42,48,50–55] As a representative example, Lee et al[55] developed an AB model of MRSA transmission across 20 acute care hospitals in Orange County, California. When discharged patients returned to the community, they could be readmitted to any hospital in the region, thus providing a pathway for MRSA to spread from one hospital to another. This example illustrates the ability of AB models to capture transmission dynamics at individual, facility, and regional levels. These types of studies demonstrate the value of mathematical modeling as a tool for informing national or international efforts to control the spread of infectious pathogens. In addition, many of these studies leverage hybrid modeling approaches that combine compartmental and AB approaches in such a way as to exploit the advantages of each technique.[56–58]

MAJOR TAKE-HOME POINTS

Most studies using mathematical modeling in HE&AS consist of the application of either compartmental or AB modeling to simulate transmission and evaluate potential interventions. Successful modeling efforts often leverage close collaboration between modeling and practitioner expertise and include thorough validation and calibration prior to experimentation and analysis. In addition, striking the balance between model simplicity and complexity is an important consideration. Regardless of the specific modeling methodology, mathematical models should focus on providing actionable decision support to healthcare epidemiologists and antibiotic stewards. To achieve this objective, and in light of the limitations and pitfalls summarized above, we propose a set of best practices for developing mathematical models (Table 2).

CONCLUSIONS

Mathematical modeling is a valuable methodology for providing insight into relevant problems in HE&AS. It is a complementary approach, one that provides a unique perspective relative to more traditional methods, such as randomized controlled trials. In many cases, mathematical models can be used to validate or mediate results found by observational or experimental methods; in other cases, mathematical models may provide insight that cannot be obtained via these more

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traditional approaches. In that sense, models are not intended to replace evidence produced by real-world clinical studies; instead, they can be used to explore a range of scenarios and interventions and to generate subsequent hypotheses that can provide clues to researchers and decision-makers faced with seemingly unlimited HE&AS intervention strategies but limited resources to implement and test them. With improved rigor and efforts to better leverage improvements in computational resources, mathematical modeling should play a significant role in future studies in this field.

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Address correspondence to Sean L. Barnes, PhD, Department of Decision, Operations & Information Technologies, Robert H. Smith School of Business, University of Maryland, 4352 Van Munching Hall, 7699 Mowatt Ln, College Park, MD 20742-1815 (sbarnes@rhsmith.umd.edu).

REFERENCES

1. Bonten MJ, Austin DJ, Lipsitch M. Understanding the spread of antibiotic resistant pathogens in hospitals: mathematical models as tools for control. *Clin Infect Dis* 2001;33:1739–1746.
2. Caro JJ, Briggs AH, Siebert U, Kuntz KM, ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling good research practices—overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Med Decis Making* 2012;32: 667–677.
3. Doan TN, Kong DC, Kirkpatrick CM, McBryde ES. Optimizing hospital infection control: the role of mathematical modeling. *Infect Control Hosp Epidemiol* 2014;35:1521–1530.
4. Grundmann H, Hellriegel B. Mathematical modelling: a tool for hospital infection control. *Lancet Infect Dis* 2006;6:39–45.
5. Opatowski L, Guillemot D, Boelle PY, Temime L. Contribution of mathematical modeling to the fight against bacterial antibiotic resistance. *Curr Opin Infect Dis* 2011;24:279–287.
6. van Kleef E, Robotham JV, Jit M, Deeny SR, Edmunds WJ. Modelling the transmission of healthcare associated infections: a systematic review. *BMC Infect Dis* 2013;13:294.
7. Keeling MJ, Rohani P. *Modeling Infectious Diseases in Humans and Animals*. Princeton: Princeton University Press; 2008.
8. Vynnycky E, White RG. *An Introduction to Infectious Disease Modelling*. New York: Oxford University Press; 2010.
9. Grassly NC, Fraser C. Mathematical models of infectious disease transmission. *Nat Rev Microbiol* 2008;6:477–487.
10. Riley S. Large-scale spatial-transmission models of infectious disease. *Science* 2007;316:1298–1301.
11. North MJ, Collier NT, Vos JR. Experiences creating three implementations of the repast agent modeling toolkit. *ACM Trans Model Comput Simul* 2006;16:1–25.
12. AnyLogic. The AnyLogic Company website. http://www.xjtek.com. Published 2012. Accessed May 1, 2016.
13. NetLogo. The NetLogo website. http://ccl.northwestern.edu/netlogo/. Published 1999. Accessed May 1, 2016.
14. Sterman JD. Systems dynamics modeling: tools for learning in a complex world. *IEEE Eng Manag Rev* 2002;30:42–42.
15. Rahmandad H, Sterman J. Heterogeneity and network structure in the dynamics of diffusion: comparing agent-based and differential equation models. *Manag Sci* 2008;54:998–1014.
16. An G. Agent-based computer simulation and SIRs: building a bridge between basic science and clinical trials. *Shock* 2001;16: 266–273.
17. Gu W, Killeen GF, Mbogo CM, Regens JL, Githure JI, Beier JC. An individual-based model of *Plasmodium falciparum* malaria transmission on the coast of Kenya. *Trans R Soc Trop Med Hyg* 2003;97:43–50.
18. Hotchkiss JR, Strike DG, Simonson DA, Broccard AF, Crooke PS. An agent-based and spatially explicit model of pathogen dissemination in the intensive care unit. *Crit Care Med* 2005;33: 168–176.
19. Zorzenon dos Santos RM, Coutinho S. Dynamics of HIV infection: a cellular automata approach. *Phys Rev Lett* 2001;87:168102.
20. Kasaie P, Andrews JR, Kelton WD, Dowdy DW. Timing of tuberculosis transmission and the impact of household contact tracing: an agent-based simulation model. *Am J Respir Crit Care Med* 2014;189:845–852.
21. Macal CM, North MJ. Toward teaching agent-based simulation. In: *Proceedings of the 2010 Winter Simulation Conference (WSC)*. Baltimore: WSC; 2010.
22. Kasaie P, Kelton WD. Guidelines for design and analysis in agent-based simulation studies. In: *Proceedings of the 2015 Winter Simulation Conference: Social and Behavioral Simulation*. Piscataway, NJ: IEEE Press; 2015.
23. Austin DJ, Anderson RM. Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models. *Philos Trans R Soc Lond B Biol Sci* 1999;354: 721–738.
24. Beggs CB, Noakes CJ, Shepherd SJ, Kerr KG, Sleigh PA, Banfield K. The influence of nurse cohorting on hand hygiene effectiveness. *Am J Infect Control* 2006;34:621–626.
25. Beggs CB, Shepherd SJ, Kerr KG. Increasing the frequency of hand washing by healthcare workers does not lead to commensurate reductions in staphylococcal infection in a hospital ward. *BMC Infect Dis* 2008;8:114.
26. D'Agata EM, Horn MA, Ruan S, Webb GF, Wares JR. Efficacy of infection control interventions in reducing the spread of multidrug-resistant organisms in the hospital setting. *PLOS ONE* 2012;7:e30170.
27. D'Agata EM, Magal P, Olivier D, Ruan S, Webb GF. Modeling antibiotic resistance in hospitals: the impact of minimizing treatment duration. *J Theor Biol* 2007;249:487–499.
28. Sebille V, Chevret S, Valleron AJ. Modeling the spread of resistant nosocomial pathogens in an intensive-care unit. *Infect Control Hosp Epidemiol* 1997;18:84–92.
29. Austin DJ, Bonten MJ, Weinstein RA, Slaughter S, Anderson RM. Vancomycin-resistant enterococci in intensive-care hospital settings: transmission dynamics, persistence, and the impact of infection control programs. *Proc Natl Acad Sci U S A* 1999;96: 6908–6913.
30. Cooper BS, Medley GF, Scott GM. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. *J Hosp Infect* 1999;43:131–147.
31. Cooper BS, Medley GF, Stone SP, et al. Methicillin-resistant *Staphylococcus aureus* in hospitals and the community: stealth

dynamics and control catastrophes. *Proc Natl Acad Sci U S A* 2004;101:10223–10228.
32. Grundmann H, Hori S, Winter B, Tami A, Austin DJ. Risk factors for the transmission of methicillin-resistant *Staphylococcus aureus* in an adult intensive care unit: fitting a model to the data. *J Infect Dis* 2002;185:481–488.
33. McBryde ES, Pettitt AN, McElwain DL. A stochastic mathematical model of methicillin resistant *Staphylococcus aureus* transmission in an intensive care unit: predicting the impact of interventions. *J Theor Biol* 2007;245:470–481.
34. Robotham JV, Jenkins DR, Medley GF. Screening strategies in surveillance and control of methicillin-resistant *Staphylococcus aureus* (MRSA). *Epidemiol Infect* 2007;135:328–342.
35. Bootsma MC, Diekmann O, Bonten MJ. Controlling methicillin-resistant *Staphylococcus aureus*: quantifying the effects of interventions and rapid diagnostic testing. *Proc Natl Acad Sci U S A* 2006;103:5620–5625.
36. Forrester M, Pettitt AN. Use of stochastic epidemic modeling to quantify transmission rates of colonization with methicillin-resistant *Staphylococcus aureus* in an intensive care unit. *Infect Control Hosp Epidemiol* 2005;26:598–606.
37. Laskowski M, Demianyk BCP, Witt J, Mukhi SN, Friesen MR, McLeod RD. Agent-based modeling of the spread of influenza-like illness in an emergency department: a simulation study. *IEEE Trans Inf Technol Biomed* 2011;15:877–889.
38. Barnes S, Golden B, Wasil E. MRSA transmission reduction using agent-based modeling and simulation. *INFORMS J Comput* 2010;22:635–646.
39. Barnes SL, Morgan DJ, Harris AD, Carling PC, Thom KA. Preventing the transmission of multidrug-resistant organisms: modeling the relative importance of hand hygiene and environmental cleaning interventions. *Infect Control Hosp Epidemiol* 2014;35:1156–1162.
40. Meng Y, Davies R, Hardy K, Hawkey P. An application of agent-based simulation to the management of hospital-acquired infection. *J Simulat* 2010;4:60–67.
41. Jaramillo C, Taboada M, Epelde F, Rexachs D, Luque E. Agent based model and simulation of MRSA transmission in emergency departments. *Procedia Comput Sci* 2015;51:443–452.
42. Lee BY, Singh A, Bartsch SM, et al. The potential regional impact of contact precaution use in nursing homes to control methicillin-resistant *Staphylococcus aureus*. *Infect Control Hosp Epidemiol* 2013;34:151–160.
43. Macal CM, North MJ, Collier N, et al. Modeling the transmission of community-associated methicillin-resistant *Staphylococcus aureus*: a dynamic agent-based simulation. *J Transl Med* 2014;12:124.
44. Rubin MA, Jones M, Leecaster M, et al. A simulation-based assessment of strategies to control *Clostridium difficile* transmission and infection. *PLOS ONE* 2013;8:e80671.
45. Barnes S, Golden B, Wasil E, Furuno J, Harris A. An application of factorial design to compare the relative effectiveness of hospital infection control measures. In: Jain S, Creasey RR, Himmelspach J, White KP, Fu M, eds., *Proceedings of the 2011 Winter Simulation Conference*, 2011; 1283–1294.
46. Montville R, Chen Y, Schaffner DW. Risk assessment of hand washing efficacy using literature and experimental data. *Int J Food Microbiol* 2002;73:305–313.
47. Eubank S, Guclu H, Kumar VS, et al. Modelling disease outbreaks in realistic urban social networks. *Nature* 2004;429:180–184.
48. Barnes SL, Harris AD, Golden BL, Wasil EA, Furuno JP. Contribution of interfacility patient movement to overall methicillin-resistant *Staphylococcus aureus* prevalence levels. *Infect Control Hosp Epidemiol* 2011;32:1073–1078.
49. Hetem DJ, Bootsma MC, Bonten MJ. Prevention of surgical site infections: decontamination with mupirocin based on preoperative screening for *Staphylococcus aureus* carriers or universal decontamination? *Clin Infect Dis* 2016;62:631–636.
50. Lee BY, Wong KF, Bartsch SM, et al. The Regional Healthcare Ecosystem Analyst (RHEA): a simulation modeling tool to assist infectious disease control in a health system. *J Am Med Inform Assoc* 2013;20:e139–e146.
51. Slayton RB, Toth D, Lee BY, et al. Vital signs: estimated effects of a coordinated approach for action to reduce antibiotic-resistant infections in health care facilities— United States. *MMWR Morb Mortal Wkly Rep* 2015;64:826–831.
52. Smith DL, Dushoff J, Perencevich EN, Harris AD, Levin SA. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: resistance is a regional problem. *Proc Natl Acad Sci U S A* 2004;101:3709–3714.
53. Bartsch SM, Huang SS, Wong KF, Avery TR, Lee BY. The spread and control of norovirus outbreaks among hospitals in a region: a simulation model. *Open Forum Infect Dis* 2014;1:ofu030.
54. Lee BY, Bartsch SM, Wong KF, et al. Simulation shows hospitals that cooperate on infection control obtain better results than hospitals acting alone. *Health Aff (Millwood)* 2012;31:2295–2303.
55. Lee BY, McGlone SM, Wong KF, et al. Modeling the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) outbreaks throughout the hospitals in Orange County, California. *Infect Control Hosp Epidemiol* 2015;32:562–572.
56. Bobashev GV, Goedecke DM, Feng Y, Epstein JM. A hybrid epidemic model: combining the advantages of agent-based and equation-based approaches. In: Henderson SG, Biller B, Hsieh M-H, Shortle J, Tew JD, Barton RR, eds., *Proceedings of the 2007 Winter Simulation Conference*, 2007; 1532–1537.
57. Swinerd C, McNaught KR. Design classes for hybrid simulations involving agent-based and system dynamics models. *Simul Model Pract Theory* 2012;25:118–133.
58. Yu B, Wang J, McGowan M, Vaidyanathan G, Younger K. Gryphon: a hybrid agent-based modeling and simulation platform for infectious diseases. In: Chai S-K, Salerno J, Mabry P, eds., *Advances in Social Computing*. Vol. 6007. Berlin: Springer; 2010:199–207.
59. Wikipedia. Comparison of system dynamics software. https://en.wikipedia.org/wiki/Comparison_of_system_dynamics_software. Published 2016. Accessed May 31, 2016.
60. System Dynamics Society. Tools for system dynamics. http://tools.systemdynamics.org. Published 2016. Accessed May 31, 2016.
61. Wikipedia. Comparison of agent-based modeling software. https://en.wikipedia.org/wiki/Comparison_of_agent-based_modeling_software. Published 2016. Accessed May 31, 2016.
62. Agent-based models methodology and philosophy. Simulators. http://www.agent-based-models.com/blog/resources/simulators/. Published 2016. Accessed May 31, 2016.
63. Allan B. Survey of agent based modeling and simulation tools v1.1. http://www.grids.ac.uk/Complex/ABMS/. Published 2010. Accessed May 31, 2016.

https://doi.org/10.1017/ice.2016.160 Published online by Cambridge University Press