

## Editorial

# The Calculus of Transmission

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*Model building is the art of selecting those aspects of a process that are relevant to the question being asked.*

—JH Holland<sup>1</sup>

Models are used to explain complexity in the real world. Models are useful insofar as they provide some understanding of reality and our collective experience. To illustrate, professionals responsible for the control of nosocomial infections in healthcare institutions employ a variety of barrier techniques to prevent the spread of transmissible pathogens. These techniques are extrapolated from models that describe our understanding of the processes of transmission. The models are based on the empirical observations of experts and often lack explicit, objective evidence to validate the model. Nevertheless, the models provide an understanding of current reality and support a belief system that determines our behavior when confronted with the complex circumstances surrounding transmission of nosocomial pathogens.

Models that undergird our beliefs and behaviors may be more or less explicit. One of the early efforts to use explicit mathematical models to describe disease transmission was that described by Sir Ronald Ross in 1911.<sup>2</sup> Ross was a parasitologist and epidemiologist who described the malaria life cycle. Based on

his careful studies of the life cycle of malaria in humans and mosquitoes, Ross developed a mathematical model of transmission. From that explicit model, he deduced that malaria could be controlled by environmental interventions that eradicate mosquitoes. This idea initially was met with skepticism. When the hypothesis was put to the test, it resulted in the control of a disease that was—and is—a major source of human morbidity and mortality in many parts of the world. Subsequent efforts to generate mathematical models to illumine understanding of disease transmission were received with mixed enthusiasm. Parasitologists were responsible for much of the early work with mathematical models of transmission.<sup>3</sup> Because of the complex transmission systems inherent in parasite life cycles (eg, schistosomiasis), mathematical theory often was so disconnected from reality that epidemiologists became disenchanted with efforts to describe diseases with theoretical mathematical models.

Sébille, Chevret, and Valleron<sup>4</sup> describe an explicit mathematical model of the transmission of a resistant nosocomial pathogen in this issue of *Infection Control and Hospital Epidemiology*. Based on assumptions derived from the medical literature regarding probabilities of transmission and colonization for methicillin-resistant *Staphylococcus aureus*

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(MRSA), the authors have generated a model of transmission in an intensive-care unit (ICU). The purpose of the model is to predict the benefits of alternative measures for controlling the transmission of nosocomial pathogens. How does this model enlighten our understanding of transmission in the circumstances described? What are the strengths and weaknesses of the model?

For “calculus-challenged” readers, which includes the author of this editorial, the first impulse is to disregard the article as irrelevant, because the mathematical theory is incomprehensible. A second, and perhaps more risky, impulse is to assume that any author capable of generating such intimidating mathematical equations must have an unassailable handle on the truth. Readers should be guided by neither impulse. The obscure mathematical equations are indeed the least important attribute of the manuscript. Rather, the value of the authors’ model depends on the ability of the model to predict the success of alternative intervention strategies when implemented in real-world situations. The predictive value of the model depends on how well the authors have understood, defined, and translated reality into mathematical theory. Therefore, the reader should critically examine the assumptions on which the model is constructed. The veracity of the model depends more on the validity of the assumptions than on the arcane mathematical equations.

The unfamiliar reader will discover that the explicit mathematical model described by the authors is based on a series of assumptions. The assumptions are estimated from ranges of values derived from the current literature. The authors correctly have examined a range of assumptions (sensitivity analysis) rather than limiting the analysis to static estimates. For example, the authors cite references describing estimates of compliance with handwashing among physicians and staff, and analyze the model over the range of estimates of the probability of compliance. The analysis enables the authors to estimate the impact of compliance on MRSA colonization rates among staff and patients.

A careful review of the assumptions in the model reveals several interesting observations. First, we often presume that the complex dynamics of transmission of pathogens have been studied exhaustively. When confronted with the requirement to produce objective measurements for the multiple steps in the transmission process, we discover how little actually is known about these complex processes. Second, it is obvious that some assumptions do not reflect reality. For example, to assume that the number of staff members and patients in the ICU are con-

stant over time would be incorrect. However, it is necessary to simplify some assumptions to generate the model. Although one might account for this dynamic fluctuation in the population within the theoretical model, it would add significant complexity and probably contribute little to the understanding of variation in colonization rates. These assumptions do not diminish the veracity of the model.

On the other hand, some assumptions that the authors made in constructing the model call to question how effectively the model reflects reality. The model describing transmission of pathogens in the ICU was constructed with colonization as the outcome of interest (dependent variable). The hypothesis derived from the model suggests that the most effective intervention for controlling colonization is to restrict admissions of colonized patients to the ICU. The model makes no attempt to account for the benefits of admission to the ICU. Furthermore, there is an implicit assumption that a relatively high proportion of colonized patients will develop infection, resulting in additional morbidity and perhaps mortality. In the absence of this assumption, colonization itself would be an insufficient reason to deny access to the potential benefits of care in the ICU. The model also assumes that rapid microbiologic screening tools are available and that the tools are characterized by high levels of sensitivity, specificity, and predictive value. Without such tools, it would be impossible to identify rapidly colonized patients requiring urgent admission to the ICU. The reader must evaluate these assumptions critically and decide how far the model strays from reality and to what degree the assumptions limit its applicability.

Do these assumptions nullify the utility of the model of transmission proposed by the authors? Not necessarily, for the model simply suggests that, under the stated assumptions and based on the three alternative strategies for controlling the problem, restricting admissions to the ICU provides the most effective strategy for controlling the problem. The model has generated a testable hypothesis. Using models to generate hypotheses regarding transmission can provide useful and unexpected results. Koopman and colleagues<sup>5,6</sup> have developed dynamic, nonlinear transmission models for human immunodeficiency virus (HIV) infection that have generated unanticipated hypotheses regarding the efficacy of HIV vaccines. The models suggest that vaccines that reduce the transmissibility of HIV—while providing no measurable protection for the infected host—would reduce disease significantly within a population. The explicit model of transmission generated by Koopman has contributed to a

change in paradigms regarding the assessment of the effectiveness of HIV vaccines.

Ross<sup>2</sup> was successful in incorporating mathematical models in the study of malaria because he understood the dynamics of transmission, constructed a relatively simple model that accurately described transmission, deduced from the model an hypothesis regarding control of transmission, and tested the hypothesis in the field. Sébille, Chevret, and Valleron<sup>4</sup> have generated an explicit mathematical model that more or less describes transmission of nosocomial pathogens in a closed hospital environment and have deduced an hypothesis regarding interventions to control transmission. The appropriate next step is to test the hypothesis. This will provide the ultimate test of the authors' ability to link reality with theory.

Where I take issue with the authors is their suggestion that mathematical modeling “. . . should be encouraged as a valuable tool to study the effectiveness of measures . . . when field epidemiology or intervention studies are not feasible. . . .” The mathematical model serves a purpose in generating hypotheses. However, a model is only a theoretical construct of complex real-world phenomena; therefore, the model should not be used to examine effectiveness. The effectiveness of the intervention must be examined in

the context of real-world, dynamic situations.

The calculus of transmission may offer interesting and unexpected insights into our understanding of the complexities of infectious disease transmission. Historically, the development of complex mathematical models was hampered by the intractable analyses. Modern computers have mitigated this obstacle. The success and utility of mathematical models will depend on the skills of the investigators in comprehending reality and translating that reality into theoretical models.

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