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Dynamic Transmission Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-5

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ABSTRACT

The transmissible nature of communicable diseases is what sets them apart from other diseases modeled by health economists. The probability of a susceptible individual becoming infected at any one point in time (the force of infection) is related to the number of infectious individuals in the population, will change over time, and will feed back into the future force of infection. These nonlinear interactions produce transmission dynamics that require specific consideration when modeling an intervention that has an impact on the transmission of a pathogen. Best practices for designing and building these models are set out in this article.

Keywords: dynamic transmission, best practices, infectious disease, modeling.

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Background to The Task Force

A new Good Research Practices in Modeling Task Force was approved by the ISPOR Board of Directors in 2010, and the Society for Medical Decision Making was invited to join the effort. The Task Force cochairs and members are expert developers and experienced model users from academia, industry, and government, with representation from many countries. Several teleconferences and hosted information sessions during scientific meetings of the Societies culminated in an in-person meeting of the Task Force as a whole, held in Boston in March 2011. Draft recommendations were discussed and subsequently edited and circulated to the Task Force members in the form of a survey where each one was asked to agree or disagree with each recommendation, and if the latter, to provide the reasons. Each group received the results of the survey and endeavored to address all issues. The final drafts of the seven articles were available on the ISPOR and Society for Medical Decision Making Web sites for general comment. A second group of experts was invited to formally review the articles. The comments received were addressed, and the final version of each article was prepared. (A copy of the original draft article, as well as the reviewer comments and author responses, is available at the ISPOR Web site: http://www.ispor.org/workpaper/Dynamic-Transmission-Modeling.asp.) A summary of these articles was presented at a plenary session at the ISPOR 16th Annual International Meeting in Baltimore, MD, in May 2011, and again at the 33rd Annual Meeting of the Society for Medical Decision Making in Chicago, IL, in October 2011. These articles are jointly published in the Societies' respective journals, *Value in Health* and *Medical Decision Making*. Other articles in this series [1–6] describe best practices for conceptualizing models, building and applying other types of models, and addressing uncertainty, transparency, and validations. This article addresses best practices for dynamic transmission models. Examples are cited throughout, without implying endorsement or preeminence of the articles referenced.

Introduction

The transmissible nature of communicable diseases is the critical characteristic that sets them apart from other diseases modeled by health economists [7,8]. If an intervention reduces cases in the community, then the risk to others goes down. Reduce them enough, and the infection will be eliminated and will not return unless reintroduced. Even then, it will not be able to spread unless there are sufficient susceptible individuals. Maintaining vaccination—which reduces susceptibility—at sufficiently high coverage

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(though crucially not necessarily 100%) can permanently prevent infection from spreading [7]. Thus, there are population-level effects in addition to those accruing to individuals and caregivers reached by the program. This is not so for noncommunicable diseases. For example, reducing the prevalence of heart disease makes no difference to the heart disease risk in others. If every case is treated, new cases still arise, and the overall health benefits can be estimated by summing the individual benefits. Many commonly used decision-analytic models, such as Markov models, ignore the indirect effects that arise from averted infections, whereas dynamic transmission models provide a tool to model such externalities.

This difference is fundamental and yet often overlooked by analysts. In a recent review of cost-effectiveness studies of vaccination programs, only 11% of 208 studies used an approach that could incorporate these indirect (as well as direct) effects [9]. Others have reported similar findings for other interventions against communicable diseases, including mass screening and treatment programs for chlamydia [10]. Most analysts have simply adapted the same class of model used for noncommunicable diseases, ignoring this fundamental property of communicable disease control programs. Hence, comparison across economic analyses is more difficult because results may be very sensitive to the underlying model structure. Clearly then, there is a need for specific guidance in this field.

What is a Dynamic Transmission Model?

Dynamic transmission models (often shortened to "dynamic" models) are capable of reproducing the direct and indirect effects that may arise from a communicable disease control program. They differ from other (static) models that assume a constant risk of infection (sometimes referred to as the "force of infection"): it is a function of the number of infectious individuals (or infectious particles, such as intestinal worm eggs) in the population (or environment) at a given point in time [11]. If an intervention reduces this pool of infectiousness, then the risk to uninfected susceptible individuals will decrease. That is, individuals not reached by the program can still benefit by experiencing a lower infection risk. The models used can be deterministic or stochastic; individual or cohort-based; include economic and health outcomes or be standalone epidemiological analyses; be simple explorations of the system or be very detailed with many parameters. All share the same distinguishing feature—that the infection risk is dependent on the number of infectious agents at a given point in time. These dynamic aspects will be the focus of these best practices.

Basic reproduction number

The basic reproduction number (R_0) is a fundamental metric in infectious disease epidemiology [11,12]. It is the average number of secondary infections generated by a typical case in a fully susceptible population. A closely allied metric is the effective reproduction number, $R_{e(t)}$, which does not specify that the whole population must be susceptible, defined as R_0 multiplied by the susceptible fraction of the population $s_{(t)}$ [11,12]. The reproduction number gives a measure of the disease's ability to spread in a population. A value of 1 gives a threshold for invasion of a pathogen into a population.

Malaria, for instance, now has an R_0 below 1 in northern Europe, and although most Northern Europeans are susceptible, and cases are regularly introduced via travel from endemic areas, malaria epidemics do not occur [13,14]. By contrast, severe acute respiratory syndrome had an R_0 of approximately 3 (in health care settings), and everyone was susceptible. That is, each case generated on average three other cases, and each of these would be expected to generate an average of three further cases, and so on, leading to an exponentially increasing epidemic [15]. The basic reproduction number also gives an indication of the ease of controlling an infection. It is obvious that there is no need for further control measures for malaria in northern Europe. Severe acute respiratory syndrome, on the other hand, required stringent control measures for a large epidemic to be averted.

Natural immunity is another unique feature of infectious diseases (although not all infections stimulate immunity) and is the principal reason for the depletion of susceptible individuals, leading to an epidemic slowing down and eventually declining. Dynamic transmission models typically capture this by allowing individuals who recover from infection to transition into a recovered state in which they are immune to further infection. The rate at which natural immunity is lost, returning individuals to a susceptible state, is one factor that influences a pathogen's ability to remain endemic in a population.

When is a Dynamic Approach Appropriate?

Dynamic models are important in two circumstances: 1) when an intervention impacts a pathogen's ecology, for example, by applying selection pressure resulting in "strain replacement" [16,17], and 2) when the intervention impacts disease transmission [7,8]. A static model is acceptable if target groups eligible for intervention are not epidemiologically important (e.g., evaluation of hepatitis A vaccination in travelers from low- to high-incidence countries), or when effects of immunizing a given group are expected to be almost entirely direct (e.g., vaccination of the elderly against influenza or pneumococcal disease). Static models are also acceptable when their projections suggest that an intervention is cost-effective, and dynamic effects would further enhance this (e.g., via prevention of secondary cases). Adopting such an approach, which undervalues an intervention, can lead to poor public health decision making if policymakers use such estimates to decide on the optimum allocation of a limited health care budget.

Reduced transmission does not always result in net health and economic gains; in particular, increasing age at infection may be associated with reduced health due to the changing spectrum of illness in older individuals [18]. Also, replacement effects have been reported, for example, in pneumococcal disease, that may limit health gains due to other subtypes of bacteria "substituting" those removed by vaccination. Where static models project interventions to be unattractive or borderlineattractive (i.e., close to willingness-to-pay thresholds), supplementary dynamic modeling should be undertaken to evaluate whether the inclusion of indirect herd immunity effects, replacement, and age shifts alter the projected cost-effectiveness. Although indirect effects can be incorporated by using a static framework (e.g., European countries did so by using US data [19,20] in evaluating the economic attractiveness of pneumococcal conjugate vaccines in children), the danger is that the level of indirect protection may be very different in another setting (e.g., different coverage levels). Flowcharts developed by the World Health Organization for the evaluation of immunization programs can be helpful in guiding the decision about dynamic versus static models [21].

Indirect effects of intervention programs

The best-known example of economically important indirect effects is herd immunity with large-scale vaccination programs. When coverage exceeds a critical threshold (V_c), disease is eliminated, as too few susceptible persons remain to ensure transmission. Infectious individuals will (on average) cause less than one new infection before recovering, as most contacts will be with immune individuals. As an epidemic does not occur, unvaccinated individuals experience a low infection risk. In a homogeneously mixing population (one in which all individual are equally likely to

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