

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

*Richard Pitman, PhD, David Fisman, MD, MPH, FRCPC, Gregory S. Zaric, PhD, Maarten Postma, PhD, Mirjam Kretzschmar, PhD, John Edmunds, BSc, MSc, PhD, Marc Brisson, PhD, On Behalf of the ISPOR-SMDM Modeling Good Research Practices Task Force*

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*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 paper. **Key words:** modeling; methods; dynamic transmission; good practices; infectious disease. (Med Decis Making 2012;32:712-721)*

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**A** new Good Research Practices in Modeling Task Force was constituted by the ISPOR Board of Directors in 2010, and the Society for Medical Decision Making was invited to join the effort. This paper, along with six others,<sup>1-6</sup> is part of a series commissioned by the Task Force.

Received 2 March 2012 from Oxford Outcomes, Oxford, United Kingdom (RP); the Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada (DF); Ivey School of Business, University of Western Ontario, London, Canada (GSZ); Unit of PharmacoEpidemiology and PharmacoEconomics, Department of Pharmacy, University of Groningen, Groningen, Netherlands (MP); Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, and Center for Infectious Disease Control, RIVM, Bilthoven, Netherlands (MK); Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom (JE); URESP, Centre de Recherche FRSQ du CHA Universitaire de Québec and Département de Médecine Sociale et Préventive, Laval University, Quebec City, Canada (MB). Revision accepted for publication 19 June 2012.

Address correspondence to Richard Pitman, PhD, Oxford Outcomes, Seacourt Tower, West Way, Oxford, OX2 0JJ, UK; e-mail: richard.pitman@oxfordoutcomes.com.

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## INTRODUCTION

The transmissible nature of communicable diseases is the critical characteristic that sets them apart from other diseases modeled by health economists.<sup>7,8</sup> 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 (though crucially not necessarily 100%) can permanently prevent infection from spreading.<sup>7</sup> Thus, there are population-level effects in addition

### Related Materials

For more information on the ISPOR-SMDM Task Force, visit the website at <http://www.ohsu.edu/epc/mdm/modeling.cfm>. See “Modeling Good Research Practices—Overview, Issues, and Preferred Practices: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force,” by J. Jaime Caro, Andrew H. Briggs, Uwe Siebert, and Karen M. Kuntz, published in this issue on pages 667-677, for an overview of the series.

to those accruing to individuals and caregivers reached by the program. This is not so for noncommunicable diseases. For example, reducing prevalence of heart disease makes no difference to 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.<sup>9</sup> Others have reported similar findings for other interventions against communicable diseases, including mass screening and treatment programs for chlamydia.<sup>10</sup> 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, as 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, which 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; e.g., intestinal worm eggs) in the population (or environment) at a given point in time.<sup>11</sup> 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; they can include economic and health outcomes or be stand-alone epidemiological analyses; and they can be simple explorations of the system or 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 are the focus of these best practices.

## Basic Reproduction Number

The basic reproduction number,  $R_0$ , is a fundamental metric in infectious disease epidemiology.<sup>11,12</sup> 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,  $s_{(t)}$ .<sup>11,12</sup> 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.<sup>13,14</sup> By contrast, SARS (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, 3 other cases, and each of these would be expected to generate an average of 3 further cases and so on, leading to an exponentially increasing epidemic.<sup>15</sup> 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. SARS, however, 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 that 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 affects a pathogen’s ecology, for example by applying selection pressure resulting in “strain replacement,”<sup>16,17</sup> and 2) when the intervention affects disease transmission.<sup>7,8</sup>

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 enhance this (via prevention of secondary cases, e.g.). Adopting such an approach, which undervalues an intervention, can lead to poor public health decision making if policy makers 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.<sup>18</sup> 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 borderline attractive (i.e., close to willingness-to-pay thresholds), supplementary dynamic modeling should be undertaken to evaluate whether inclusion of indirect herd immunity effects, replacement, and age shifts alter projected cost-effectiveness. Although indirect effects can be incorporated using a static framework (e.g., European countries did so in evaluating economic attractiveness of pneumococcal conjugate vaccines in children using US data<sup>19,20</sup>), 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.<sup>21</sup>

### 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 1 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 individuals are

equally likely to have contact with all other individuals and there are no preferences), for herd immunity to occur,  $V_c$  has to be greater than  $1 - 1/R_0$ .<sup>11,12</sup> Successful eradication of smallpox and elimination of many childhood infections from countries with high infant vaccination coverage have provided “proof of concept” for this relationship.

Indirect effects can also be observed for other large-scale population-based programs against communicable diseases, such as screening (e.g., population-based screening for chlamydia has effects in age and sex groups not screened<sup>22,23</sup>). Not taking these into account may lead to overly pessimistic cost-effectiveness ratios. Indirect effects may mean also that the group optimally targeted is not the one that experiences the greatest disease burden but that which contributes most to the force of infection (e.g., dynamic models, not static models, may show that immunizing younger individuals is the best means of preventing influenza-related mortality in older individuals<sup>24</sup>). Similarly, dynamic models may identify groups at less risk of sequelae as the best targets for chlamydia screening programs.<sup>22,23</sup>

Indirect effects are not always beneficial, even if they decrease infection in the population. Reducing infection risk in susceptible individuals increases the average age at which they become infected,<sup>11,12</sup> and for many diseases, this increases complication risk and mortality (e.g., hepatitis A, varicella<sup>25,26</sup>). Older age at infection may also result in higher likelihood of infection during pregnancy, with potentially devastating complications for newborns<sup>27</sup> (e.g., several countries have seen paradoxical increases in congenital rubella resulting from partial coverage with rubella vaccine, with concomitant increase in age at first infection<sup>28,29</sup>). Complex relationships may also exist between disease incidence, latent infections, and immunity in older individuals for such infections as varicella; here, vaccine programs that result in less “boosting” as a result of childhood infections may lead to surges in reactivated infection (“shingles”) in older individuals.<sup>30,31</sup> Reduced force of infection may also result in more widely spaced epidemics, which may itself have economic value, especially when future health costs and effects are discounted.<sup>12</sup> Such spacing may also complicate capacity planning. None of these phenomena are readily captured via static models. In such circumstances, dynamic models are essential.

#### Best practices

V-1 A dynamic model is needed when evaluating an intervention against an infectious disease that 1) has

an impact on disease transmission in the target population or 2) alters the frequency distribution of strains (e.g., genotypes or serotypes).

Static models can be used if the intervention is unlikely to change the force of infection (which could occur if either the targeted population or the intervention effect is very small) or to estimate the worst-case scenario when herd immunity or age shifts cannot produce negative effects. Static models cannot adequately take into account herd immunity nor age distribution shifts. Risk of infection in susceptible individuals is constant in static models, while in dynamic models, it is a function of the proportion of the population infected (which changes over time). Hence, when intervention uptake is very low (e.g., low vaccine coverage), is targeted at groups that do not have an impact on overall transmission, or does not prevent circulation of the pathogen, static and dynamic models produce similar results.<sup>7,32</sup>

Dynamic models should be used if an intervention is likely to change the force of infection by decreasing the proportion susceptible (e.g., mass vaccination), the contact rates between individuals (e.g., closing schools during a pandemic), the duration of infectiousness (e.g., antivirals), or the probability of transmission per act (e.g., antiretrovirals). Some changes in the force of infection may also be caused by changing risk behaviors in the population when perceiving a higher risk during an outbreak. By taking into account these changes, dynamic models can 1) produce nonlinear dynamics, 2) predict higher number of cases prevented, and 3) predict changes in morbidity and mortality due to age shifts. Type-specific dynamic transmission models are necessary when interventions can induce selective pressures that cause a subset of pathogen types or even other microbes to gain a competitive advantage<sup>16,33</sup> (e.g., type replacement following vaccination<sup>16,34,35</sup> and antimicrobial resistance<sup>33,36</sup>). Dynamic models must be used when decision makers are interested in local elimination of an infectious disease or eradication (i.e., global elimination).<sup>32</sup> This is possible, without reaching everyone, only with nonlinear (herd) effects. Finally, if reinfection of treated individuals depends on the prevalence of the infection in the population, as is the case in many sexually transmitted infections, dynamic models are required.<sup>22</sup>

Several schemata exist for guiding the choice,<sup>8,21,32,37,38</sup> which can significantly affect predictions.<sup>7,8,22,39</sup>

## HOW SHOULD UNCERTAINTY BE MANAGED?

### Methodological Uncertainty

Most dynamic transmission modeling has been performed using system dynamics, where transition between compartments is represented by differential equations. With increases in computing power, it has become possible to realize dynamic transmission models using agent-based approaches where each member of a population is represented individually.<sup>40-42</sup> Deterministic compartmental models are useful for modeling average behavior of disease epidemics in large populations. When stochastic effects (e.g., extinction of disease in small populations), complex interactions between behavior and disease, or distinctly nonrandom mixing patterns (e.g., movement of disease on networks) are important, stochastic agent-based approaches may be preferred. The choice of method may influence the results, and analysts and decision makers should be aware of these effects.

#### Best practices

V-2 The appropriate type of dynamic transmission model should be used, based in part on the complexity of the interactions as well as the population size and the role of chance effects. This model could be deterministic or stochastic and population or individual based. Justification for the model structure should be given.

Deterministic models—where every state variable is uniquely determined by the parameter values and previous state variable values—always give the same results for the same starting conditions and parameter values. They approximate a system's average behavior and are most appropriate when all subgroups are large. They are comparatively easy to fit to data and thus are easier to calibrate. In a stochastic model, state variables are described by probability distributions, incorporating the role of chance. This often occurs in small populations or when a subgroup is small (at an epidemic's beginning or end, e.g.)—that is, when local extinction is likely.

Population-based models track groups, while individual-based models track each individual explicitly over time. The latter treat individuals as discrete entities who, instead of moving between compartments, change their internal "state" (e.g., from susceptible to infected) based on their interactions. Given that one individual characteristic is prior history, individual-based models are particularly



useful when risk depends on past events; representation of such phenomena in population-based models, in contrast, requires many compartments. Individual-based models can incorporate population heterogeneity and have the flexibility to assess complex interventions. Disadvantages include slower speed, lack of analytical tractability, and challenges in parameterization. Individual-based models are invariably stochastic, while population-based models can be either stochastic or deterministic.

### Uncertainty in Choice of Economic Parameters

Many control programs against communicable diseases are preventative in nature and therefore often very sensitive to the discount rate and time horizon of the analysis,<sup>43</sup> as the up-front costs are usually considerable.

Many economic evaluation guidelines call for a “lifetime” horizon. However, the concept of a lifetime horizon is not well defined for dynamic models: these models often concern whole populations, which change over time due to births, deaths, and migrations, and second-order effects can persist far into the future. For example, vaccinating an individual today might prevent infection transmission several years later; individuals not infected later would accrue benefits for the remainder of their lives and potentially not infect others, who would accrue benefits for the remainder of their lives. Consistent with the rationale for using a lifetime horizon, the time horizon should be long enough to capture all effects of the intervention. Although an infinite horizon could be used to capture all these effects, such an approach may not be useful or realistic for decision making. In some cases, it is sufficient to use the lifetime of the first vaccinated cohort. In other cases, infinite time horizons can give different results to those obtained using long fixed time horizons (e.g., 75 or 100 years).<sup>44</sup> Fixed time horizons can produce artifacts (e.g., the benefits to a cohort vaccinated just before the time horizon end will not be included in the cost-effectiveness estimate, though the vaccination costs will).

#### Best practices

V-3 Conduct sensitivity analysis on the time horizon and discount rate.

Benefits and negative outcomes may vary nonmonotonically over time, making projections of economic attractiveness dependent on the time horizon chosen.<sup>32</sup> With high discount rates, the

time horizon is less important, as distant future costs, savings, and health gains add little to the total. Thus, it is recommended that modelers conduct sensitivity analysis on both the time horizon and the discount rate.<sup>8,32,43</sup>

### Structural Uncertainty

Frequently, there is uncertainty related to the biological properties and relationships that compose a disease transmission system.<sup>45</sup> For example, in modeling transmission of human papilloma virus, both susceptible–infectious–susceptible (SIS) and susceptible–infectious–removed/immune (SIR) frameworks have been used because of insufficient information about acquisition and duration of immunity after infection with a high risk HPV strain.<sup>46</sup> The presence of a (controversial) short-term immune state associated with untreated infection has led to use of susceptible–infectious–removed/immune–susceptible (SIRS) models for chlamydia, and incorporation of such a state reproduces observed “rebound” when screening programs are modeled.<sup>47,48</sup> Alternate structural assumptions may result in markedly different projections of economic attractiveness.

#### Best practices

V-4 Conduct uncertainty analyses on known key structural assumptions that may have an impact on the conclusions, or justify the omission of such analyses.

*Structural uncertainty* refers to the impact of model choice and structure on cost and effect projections, (and thus on policy decisions). Structural uncertainty may relate to transmission routes and important risk groups (by age, sex, or risk status), behavioral assumptions about contact patterns (e.g., instantaneous versus long-term partnerships, nature of mixing between age groups), immunity durability following infection, changes in host infectiousness over time, and pathogen strain competition and replacement. A decision not to include a specific variable or structure may alter results. Structural uncertainty is often ignored, despite evidence that it can have a much greater impact on results than parameter uncertainty.<sup>7,8,39,47</sup> Often, not enough is known about a system’s biological properties for precise definition of functional relationships; alternatively, several approaches may be possible to derive a model framework for a biological process. It is particularly important to consider structural uncertainty in dynamic models, as it can

be extremely influential due to nonlinear feedback effects leading to qualitatively different dynamic regimes.<sup>39,48,49</sup>

For vaccine programs, key areas of structural uncertainty relate to representation of actual timing of vaccine doses and impact of boosting. It may be difficult to distinguish effectiveness components using empirical data: vaccine “take” (probability that a vaccinated individual develops measurable immunity) from vaccine efficacy (degree of protection against infection per contact). Sexually transmitted infection models pose challenges related to explicit structural representations of partnerships (and partner concurrency), contact tracing or partner notification, and reinfection within partnerships.<sup>50</sup>

### Parameter Uncertainty

Uncertainty in parameter values can be more influential in dynamic models than in static models due to nonlinear feedback effects leading to qualitatively different dynamic regimes. It is well known that dynamic systems may display qualitatively different behavior in different parameter regions. For example, while in some regions, a stable endemic equilibrium may exist, in other regions, the system might have oscillatory or even chaotic behavior. A small shift in parameter values may move from one dynamic regime to another (e.g., transition from a disease-free state to an endemic equilibrium near  $R_0$  of 1, where small changes in parameter values can cause large changes in prevalence). Several models have evaluated nonlinear and “catastrophic” (for the pathogen) effects of interventions for hepatitis B virus and pertussis.<sup>49,51</sup> This phenomenon also has implications for intervention effectiveness. If an intervention is implemented in a situation near a threshold, the indirect effects may be very large. The same program implemented in a different parameter region may result in a linear relationship between intervention effort and effectiveness.

Accurate parameter measurement for communicable disease models is challenging. The severity of many communicable diseases of public health importance is extremely variable, and surveillance systems may capture only information on those with symptoms sufficiently severe to warrant presentation for medical care and diagnostic testing. This also complicates estimation of infection transmissibility. Thus, modeling natural history from surveillance data likely underestimates disease incidence and overestimates severity, hospitalization, and case fatality. For many communicable diseases, there is

also a disconnect between severity and effective infectiousness, as more symptomatic individuals may modify their behavior in a way that reduces transmissibility. Thus, transmission by minimally symptomatic individuals may represent a significant problem for control.<sup>52</sup> Serological studies may be used to overcome some of these challenges, as antibody responses to infection provide a relatively durable past infection record, provided that seroconversion reliably occurs upon infection. Seroprevalence curves can be used to estimate incidence among uninfected individuals according to age, sex, and other characteristics.<sup>8,53</sup>

Transmission typically depends not only on infectiousness but also on contact patterns. Empirical data on contact patterns within and between age groups derived from large population-based surveys are available for Europe.<sup>54</sup> Surveys of sexual behavior are also available for some populations, although estimates may be biased by social desirability effects and by failure to capture highly influential core groups.<sup>55</sup>

### Intervention Effectiveness

The impact of interventions is often estimated from surveillance data, which are subject to the limitations of observational studies: misidentification of random variation as a true change in incidence, the tendency of communicable diseases to evolve and oscillate with population immunity and strain variation, and confounding by unmeasured interventions or population changes.<sup>56</sup> Long-standing interventions may make identification of preintervention data problematic.

Randomized controlled trials of intervention effectiveness are preferred as a source, but one should consider under- or overestimation. When individual randomization is used, intervention effectiveness will be underestimated because indirect effects will not be captured, since clinical trials usually incorporate a tiny fraction of the population and, thus, neither control nor intervention arms experience a reduced force of infection. Trials often don't assess hard endpoints but, rather, differences in immune responses, forcing models to extrapolate to mortality and serious morbidity.

### Identification and Synthesis of Parameter Values From Published Literature

Identification of parameter values for modeling communicable diseases presents some issues. Observational outbreak studies are more likely to be

submitted for publication if they are large or costly, biasing reproductive numbers and outbreak sizes upward. Communicable disease dynamics differ across populations due to heterogeneity in geography and climate, socioeconomic status, genetics, demography, and availability of control interventions. Thus, data synthesis across multiple studies should be used cautiously and prudently to construct plausible ranges or relatively flat priors, rather than parametric distributions for stochastic simulation or sensitivity analyses.

### Calibration and Refinement of Parameter Estimates

Given the complexities of accurate parameter estimation, model calibration is important. Some authors have recognized the importance of identifiability.<sup>57</sup> It may force reestimation of uncertain or implausible parameters and may be used to generate plausible values when empirical estimates are unavailable. Furthermore, reproducing observed disease incidence, trends, or natural history helps establish a model's credibility with decision makers.

Difficulty in calibrating across multiple domains suggests that model structures, approaches, or assumptions are incorrect. While frustrating, calibration difficulties should not be glossed over or ignored. They are an important mechanism for quality control and may suggest that current understanding of the disease biology is incorrect, helping frame priorities for future research.

### Probabilistic Sensitivity Analysis

Many current recommendations call for probabilistic sensitivity analysis as part of economic evaluations. It may be challenging or inappropriate to perform this type of analysis with dynamic transmission models. In dynamic transmission models, many of the parameters related to mixing and transmission are correlated, and these correlations need to be preserved to ensure sensible models and reasonable fit to data. However, depending on the method of parameterizing the models, the correlations may not be known. If extensive data are available, it may be possible to conduct probabilistic sensitivity analysis on dynamic models (e.g., van Hoek et al<sup>44</sup>), but this is not the norm. Thus, we do not include probabilistic sensitivity analysis as part of our best practice recommendations, although future research may resolve some of the methodological challenges associated with this type of analysis.

### Best practices

V-5 When conducting sensitivity analyses, consideration of important epidemic thresholds is helpful when there is a possibility of the model exhibiting alternate behaviors.

In nonlinear dynamic transmission models, the existence of parameter space regions that characterize distinct model behaviors (e.g., epidemic spread v. extinction) complicates uncertainty analyses. Modelers should define such behaviorally distinct regions and explicitly state whether the sensitivity analysis has been confined to one region. If the sensitivity analysis encompasses more than one region, it is informative to state the probability of achieving different equilibrium states, as parameter values are varied.

## REPORTING RESULTS AND INFORMING DECISION MAKING

In addition to general guidelines for reporting the results of economic evaluations, reports of communicable disease models should provide the estimated change in burden of infection due to an intervention, as this constitutes a major motivation for the use of dynamic rather than static models. Infections can be further disaggregated according to whether they are directly or indirectly prevented, by their route of transmission (sexual, vertical, by vector, etc.), and by population subgroup, as appropriate. Other outcomes appropriate for reporting include changes in the long-run equilibrium level (incidence or prevalence) of infection, likelihood of disease elimination, and changes in  $R_e$ .

### Ensuring Transparency and Credibility

Agencies charged with assessment of novel health technologies or developing public health policy may be unaccustomed to dynamic models.<sup>58-60</sup> Knowledge translation, provision of educational opportunities, and "short courses" for professional development will ensure that end users have the skills to understand these models. Joint publication where several groups have evaluated similar policy questions using disparate approaches can help build confidence in the use of models as a tool for policy (e.g., Halloran et al<sup>61</sup>), as shown by a recently conducted appraisal of modeling tools for evaluating cost-effectiveness of various vaccines in different settings.<sup>62</sup>

Key considerations specific to transparent presentation of communicable disease models include provision of information on how effective contact rates and mixing patterns have been inferred, as these depend on model structure such that different estimates may be obtained using a common data set. There are large variations in the values for empirical, literature-derived estimates (e.g., Mossong et al<sup>63</sup> and Fenton et al<sup>64</sup>). When system dynamics models are used, the differential equations should be included as part of any publication. When agent-based models are used, the behavior of agents should be specified in detail, including movement of agents and mixing assumptions. Descriptions of movement should address whether the model makes use of geographic zones, how they are defined, and how agents move between zones. Descriptions of mixing behavior should include how new contacts are acquired, as well as the duration of partnerships. Finally, rules governing demographics should be stated (births, deaths, household formation/dissolution, etc.).

#### Best practices

V-6 If using differential equations, provide them. Tabulate all initial values and parameters if not previously published, including the mixing matrix, and supply details of the type of mixing considered.

V-7 If using agent-based model, thoroughly describe the rules governing the agents, the input parameter values, initial conditions, and all submodels.

Presentation of all parameter values is common in most cost-effectiveness analyses. The other information specified makes it possible for independent research groups to validate or reproduce published findings.

V-8 Show the transmission dynamics over time (e.g., infection and disease incidence and prevalence). When applicable, report changes in other infection-specific outcomes, such as strain replacement and the emergence of resistance to antimicrobial drugs.

This information highlights the need for and impact of dynamic models.

## SOFTWARE OPTIONS

A number of software options are available, each having its own strengths and weaknesses. Spreadsheets (e.g., Microsoft Excel) are commonly used. This environment allows rapid development, and because of the ubiquity of spreadsheet software, models developed in this environment are easy to distribute and use by a wide audience. However,

spreadsheet development suffers from two significant limitations. First, it is very difficult to change structural assumptions after they have been coded. Second, in a spreadsheet environment, the Euler method is often used to project the system of differential equations forward in time. However, this method is not as accurate as other numerical techniques.<sup>65</sup>

There are several software packages either designed or easily adapted for dynamic transmission models. This includes STELLA, by isee systems, and Berkeley Madonna. Many of these packages contain graphical user interfaces to allow rapid development and enhance communication, and most have multiple calculation options for numerical procedures. However, the modeling environments may prevent users from implementing some desired modeling assumptions. Thus, many analysts prefer to produce their own custom code in Matlab, R, C/C++, or other programming environments. This allows the greatest flexibility in terms of modeling assumptions, model calibration, uncertainty analysis, and choice of numerical techniques. However, this approach requires the most development effort, and the programs may lack transparency to those not familiar with these environments.

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