Introduction

The transmissible nature of communicable diseases is the critical characteristic that sets them apart from those diseases more commonly modelled by health economists, such as heart disease, stroke and cancer (1, 2). If an intervention reduces the number of cases in the community, then the risk to others goes down. Reduce the cases enough, and the infection will be eliminated and will not return unless it is re-introduced. Even then, it will not be able to spread unless there is a sufficient number of susceptible individuals, so maintaining vaccination – which reduces susceptibility – at a high enough coverage (though crucially not at 100%) can permanently prevent the infection from spreading (1). That is to say, there are population-level effects in addition to those that accrue to the individuals reached by the programme (the sum of the parts is greater than the whole). This is not the case for non-communicable diseases. If we reduce the prevalence of heart disease it makes no difference at all to the risk of heart disease in others in the community. If we treated every case, we would still get new cases arising. That is, apart from the impact on the quality of life of carers, there are no knock-on benefits. The overall health benefits can be simply estimated by summing the individual benefits.

This difference is fundamental and yet often overlooked by analysts. In a recent review of cost-effectiveness studies of vaccination programmes Kim and Goldie reported that only 11% of 208 studies used an approach that could incorporate these indirect (as well as direct) effects (3). Others have reported similar findings for other interventions against communicable diseases including mass screening and treatment programmes for Chlamydia (4). Most analysts have simply adapted the same class of model used for non-communicable diseases. In doing so they are ignoring a fundamental property of communicable disease control programmes – that the overall benefits are not equal to the sum of the individual effects. 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, over and above the guidance that already exists to try to improve the generalizability and comparability of economic analyses.

What is a transmission dynamic model?

Transmission dynamic models (often shortened to just “dynamic” models) are capable of reproducing the direct and indirect effects that may arise from a communicable disease control programme. They differ from other (static) models used in decision sciences in that the risk of infection (sometimes referred to as the “force of infection”) is a function of the number of infectious individuals (or infectious particles, such as eggs of intestinal worms) in the population (or environment) at a given point in time (5). If an intervention reduces this pool of infectiousness then the risk to uninfected susceptible individuals will decrease. That is, individuals who were not reached by the programme can still benefit by experiencing a lower risk of infection. The models used can be deterministic or stochastic, individual or population-based (see later for definitions of these terms), they may include (or be linked to) an economic and health outcomes component, or may be stand-alone epidemiological analyses, they may be simple explorations of the system or very detailed with large numbers of parameters. However, all these models share the same distinguishing feature – that the risk of infection is dependent on the number of infectious agents at a given point in time. Other aspects of these models are similar to models more commonly used in health economics and decision-sciences. For this
reason, these dynamic aspects (which arise from the communicable nature of the diseases in question) will be the focus of this review. Readers are asked to refer to other papers in this series for more general advice pertaining to model-based health economic analysis.

**Basic reproduction number**

The basic reproduction number is a fundamental metric in infectious disease epidemiology (5, 6). 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, which does not specify that the whole population must be susceptible. The effective reproduction number \(R_e(t)\) is simply the basic reproduction number \(R_0\) multiplied by the fraction of the population who are susceptible \(s(t)\) (5, 6). The reproduction number gives a measure of the ability of the disease to spread in a population. A reproduction number of 1 gives a threshold for invasion of a pathogen into a population.

Malaria, for instance, now has a reproduction number below one in northern Europe, and although most Northern Europeans are susceptible to disease, and cases are regularly introduced via travel from endemic areas, malaria epidemics do not occur (7, 8). By contrast SARS had a basic reproduction number of around 3 (in healthcare settings), and everyone was susceptible. That is, each case generated about 3 other cases, and each of these would be expected to generate about 3 other cases, and so on, leading to an exponentially increasing epidemic (9). The basic reproduction number also gives an indication of the ease of control of an infection. Returning to the malaria in northern Europe example, it is obvious that there is no need for further control measures as an epidemic will not arise. SARS, on the other hand, required stringent control measures for a large epidemic to be averted.

**When is a dynamic approach appropriate?**

Dynamic models are important in two general circumstances: (i) when an intervention impacts on the ecology of a pathogen, for example by applying selection pressure resulting in “strain replacement” (10, 11), and (ii) when the intervention impacts disease transmission (1, 2). A static model is acceptable if eligible target groups for intervention are not epidemiologically important (e.g., evaluation of hepatitis A vaccination in travellers from low- to high-incidence countries), or when effects of immunising 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 static model projections suggest that an intervention will be cost-effective, with cost-effectiveness expected to be further enhanced via (excluded) dynamic effects (e.g., via prevention of secondary “add-on” cases). If such an approach is adopted, it should be born in mind that undervaluing an intervention can lead to poor public health decision making, if policy makers use such estimates of cost-effectiveness to decide on the optimum allocation of a limited healthcare budget.

Furthermore, it is important to acknowledge that not all effects associated with reduced transmission result in net health and economic gains; in particular, increasing age at infection (as described below) may be associated with reduced health due to the changing spectrum of illness in older individuals (12). Also, replacement effects have been reported, for example, in pneumococcal disease, that may reduce health or limit health gains due to other (sub) types of bacteria “substituting” those removed by vaccination. Where static models project interventions to be unattractive or borderline-attractive, supplementary dynamic modelling should be undertaken to evaluate whether inclusion of indirect effects of herd immunity, replacement and age shifts alter projected cost-effectiveness. Indirect intervention
effects can be incorporated using a static framework; for example, such an approach was used by European countries in evaluating the economic attractiveness of pneumococcal conjugate vaccines in children; static models incorporated herd-level impacts derived from US data (13, 14). However, the danger of this approach is that the level of indirect protection may be very different in a different setting (with, for instance, different levels of vaccine coverage). Flow-charts have been developed by the World Health Organization; these can be helpful in guiding the decision as to whether or not dynamic models are appropriate (15).

**Indirect effects of intervention programmes**

The best-known example of economically important indirect effects is herd immunity with large-scale vaccination programmes. When coverage exceeds a critical threshold ($V_c$) disease is eliminated, as too few susceptible persons remain to ensure persistent 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 in a population experience a low risk of infection. For herd immunity to occur, $V_c$ has to be greater than $1 / R_0$ (5, 6). Successful eradication of smallpox from the world and elimination of many childhood infections from countries with high infant vaccination coverage have provided “proof of concept” for this relation.

Indirect effects can also be observed for other large-scale population based intervention programmes against communicable diseases, such as population screening (16, 17). For example population based screening for Chlamydia infections clearly also has effects in age and gender groups not directly targeted for screening (16, 17). Not taking those effects into account when evaluating the effectiveness of a programme may lead to overly pessimistic cost-effectiveness ratios. Indirect effects also may mean that the optimal age or gender class to which interventions should be targeted is not the class that experiences the greatest burden of disease, but that which contributes most to force-of-infection; for example, immunizing younger individuals may be identified as the most attractive means of preventing influenza-related mortality in older individuals in dynamic models, but not in static models (18). Similarly, dynamic models may identify age and gender groups at less risk of sequelae as the best targets for Chlamydia screening programs (16, 17).

As mentioned, indirect effects are not always beneficial, even when they lead to decreased incidence of infection in the population. Reducing the risk of infection in susceptible individuals increases the average age at which susceptible individuals become infected (5, 6), and for many communicable diseases, this increases the risk of complications and mortality. Infectious diseases that may be more severe in older individuals include hepatitis A virus infection, SARS, and varicella (19-21). Older age at infection may also result in higher likelihood of infection during pregnancy, with devastating complications for newborns (22); several countries have seen paradoxical increases, for example, in congenital rubella infections resulting from partial population coverage with rubella vaccine, with concomitant increase in age at first infection (23, 24). 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” of the population as a result of infection in children may lead to surges in reactivated infection (“shingles”) in older individuals (25, 26). Lastly, reduced force-of-infection may result in epidemics being more widely spaced, a phenomenon which may itself have economic value, especially when future health costs and effects are subjected to discounting (6). None of these phenomena is readily captured via static models.
How should uncertainty be managed?

**Methodological uncertainty**

Historically, most dynamic transmission modelling has been performed using system dynamics models, where transition between compartments is represented by differential equations. With the increase in readily available computing power, it has become possible to realize dynamic transmission models using agent-based approaches where each member of a population is represented individually (27-29). Deterministic compartmental models are useful for modelling average behaviour of disease epidemics in large populations. When stochastic effects (e.g., extinction of disease in small populations), complex interactions between behaviour and disease, or distinctly non-random mixing patterns (e.g., movement of disease on networks) are important, agent-based approaches may be preferred. The choice of modelling method may influence the results, and analysts and decision-makers should be aware of the effects these different choices may have (see recommendations section for further advice).

As with non-infectious diseases, the assumed discount rate, and the time horizon of the analysis may be influential. Many control programmes against communicable diseases are preventative in nature (vaccines being the classic example). They are therefore often very sensitive to these methodological choices as the up-front costs of setting up a programme are usually considerable.

**Structural uncertainty**

Both static and dynamic models have to deal with uncertainty pertaining to exact model formulation, or "structural uncertainty". Frequently there is uncertainty related to the exact biological properties and relationships that comprise a disease transmission system. For example, in modelling the transmission of human papilloma virus both “susceptible-infectious-susceptible” (SIS) and “susceptible-infectious-removed/immune” (SIR) frameworks have been used, because not enough information about acquisition and duration of immunity after infection with a high risk HPV strain is available (30). The presence of a (controversial) short-term immune state associated with untreated infection has led to the use of SIRS models for Chlamydia, and incorporation of such a state reproduces observed “rebound” when screening programs are modelled (31, 32). Alternate structural assumptions may result in markedly different projections of economic attractiveness.

**Parameter uncertainty**

Uncertainty in parameter values can be more influential in dynamic models than in static models due to non-linear feedback effects leading to qualitatively different dynamic regimes. It is well known that dynamical systems may display qualitatively different behaviour in different parameter regions. For example, while in some regions a stable endemic equilibrium may exist, in other regions the system might have oscillatory behaviour or even chaotic behaviour. It may only need a small shift in parameter values to move from one dynamic regime to another. The best-known example in epidemic models is the transition from a disease free state to an endemic equilibrium when the basic reproduction number crosses the threshold value one. Near this threshold, small changes in parameter values can cause large changes in prevalence. Several recent models have evaluated non-linear, and “catastrophic” (for the pathogen) effects of interventions for hepatitis B virus and pertussis (33, 34). This phenomenon also has implications for intervention effectiveness. If an intervention is implemented in a situation near such a threshold, the indirect effects
may be very large. The same programme implemented in a different region of parameter space may result in a more or
less linear relationship between intervention effort and effectiveness.

Several challenges exist in the accurate measurement of parameters for communicable disease models. Many
communicable diseases of public health importance are extremely variable in their severity, and surveillance systems
may capture only information on infected individuals with symptoms sufficiently severe to warrant presentation for
medical care and diagnostic testing. As such, modelling the natural history of communicable diseases from public
health surveillance data is likely to result in underestimation of disease incidence, and overestimation of severity,
hospitalization risk, and case-fatality. For many communicable diseases, there is also a disconnect between severity of
illness and effective infectiousness of an individual, as more symptomatic individuals may modify their behaviour in a
way that reduces transmissibility. Thus transmission of infection by individuals who are minimally symptomatic may
represent a fundamental property of “uncontrollable” communicable diseases (35). Serological studies may be used to
overcome some of the challenges presented by case reporting, as antibody responses to infection provide a relatively
durable record of an individual’s past infection status. Seroprevalence curves can be used to estimate incidence among
uninfected individuals according to age, gender, and other characteristics (6, 36).

For most communicable diseases, transmission of infection depends not only on the infectiousness of a case,
but on contact patterns as well. Empirical data on contact patterns within and between age groups, derived from large
population-based surveys, are available for Europe, with the recently published POLYMOD study (37). Surveys of sexual
behaviour are also available for some populations (such as NATSAL in the UK), and are invaluable for parameterising
models of STI transmission although estimates may be biased by social desirability effects, and by the failure to capture
highly influential core groups (38).

Challenges in Parameter Measurement—Intervention Effectiveness

The impact of interventions (e.g., effectiveness of a vaccination or screening program) is often estimated from
quasi-experimental data derived from surveillance sources. Such data sources are subject to all of the limitations of
quasi-experiment. Misidentification of random variation as a true change in incidence, the natural tendency of
communicable diseases to evolve and oscillate as a result of population immunity and strain variation, and confounding
by unmeasured interventions or changes in the population may all potentially result in misidentification of an
intervention’s effectiveness (39). The fact that such interventions may be longstanding may make identification of pre-
intervention data problematic.

Randomized controlled trials of intervention effectiveness are preferred as a source of model effectiveness
parameters, but should consider the possible under- or over-estimation of intervention effectiveness commonly seen
with randomized trials of vaccination programs and other interventions when the disease under consideration is
communicable. When individual randomization is used, intervention efficacy and effectiveness will be underestimated,
as indirect effects will not be captured as typically neither the control nor intervention arms experience a reduced force
of infection, as clinical trials are usually tiny in comparison to the overall population. Additionally, it should be noted
that mostly models extrapolate from intermediate endpoints often measured on the level of immunity (antigens, viral
loads, infections) towards “hard” endpoints on mortality and serious morbidity, as randomized controlled trials often
lack the capability of signalling significant differences in hard endpoints whereas they do have the power to detect differences in immune responses.

Identification and Synthesis of Parameter Values from Published Biomedical Literature

Identification of parameter values for modelling of communicable diseases should follow best practices for non-communicable diseases [cite other ISPOR working paper]. It should be noted that observational studies of outbreaks are more likely to be submitted for publication if they are large and/or costly; as such, estimates of reproductive numbers and outbreak sizes derived from descriptive studies are likely to be higher than is the case in reality. A second area of complexity relates to the likelihood that communicable diseases will have different dynamics in different populations, due to heterogeneity in geography and climate, socioeconomic status, population genetics and demographic structures, and the availability of control interventions. As such, methods for data synthesis across multiple studies should be used with caution, and it may be prudent to use literature-derived parameter estimates to construct plausible ranges or relatively flat priors, rather than parametric distributions for the purposes of stochastic simulation or sensitivity analyses.

Calibration and Refinement of Parameter Estimates

Given the complexities of accurate parameter estimation, model calibration is of great importance for several reasons. Well-calibrated models may force the re-estimation of uncertain or implausible parameters, and calibration may be used to generate plausible parameter values when no empirical estimates are available. Furthermore, well-calibrated models that reproduce observed disease incidence, trends, or natural history are extremely important for the establishment of a model’s credibility with decision makers.

Difficulty in calibrating a disease model across multiple domains may suggest that model structures, approaches or assumptions are incorrect. While frustrating for the modeller, difficulties in calibration should not be glossed over or ignored, as they represent an important mechanism for quality control; furthermore, difficulty in calibration may suggest that the best current understanding of the biology of a given disease is incorrect. Consequently, models that are difficult to calibrate may provide important information that helps frame priorities for future research.

Reporting results and informing health care and public health decision making

Numerous guidelines exist for reporting the results of economic evaluations [e.g., cite other ISPOR guidelines]. These emphasize the need to present disaggregated costs (e.g., showing drug costs, hospital costs and indirect costs separately) and to show the incremental health and economic impact separately before calculating an ICER. Such guidelines apply equally to health-economic analyses of communicable disease control interventions, but this group also suggests that analyses report the estimated change in the burden of infection as a result of the intervention, as this constitutes a major motivation for the use of dynamic rather than static modelling methods. Infections can be further disaggregated according to directly or indirectly prevented infections, route of transmission (e.g., sexual, vertical, by vector, etc.), and population subgroups as appropriate.
Other outcomes specific to communicable disease-related models which are appropriate for reporting include changes in the long-run equilibrium level (incidence or prevalence) of infection; likelihood of disease elimination; and changes in the effective reproductive number of the disease.

Ensuring Transparency and Credibility

Transparency of the modeling process and results are necessary for peer review and knowledge translation, and to make models credible to decision-makers. The following steps will serve to enhance the transparency of communicable disease models: clear statements about model quality, data quality and sources, model structure and validation, extensive sensitivity analyses, and clear, candid statements of limitations. Many of these are issues discussed in general elsewhere. We focus below on those aspects that are specific to communicable disease models.

Authorities and agencies charged with the assessment of novel interventions and programs for communicable diseases may overlap with those assessing interventions for non-communicable diseases. For non-communicable diseases often less complex models suffice as compared to those used for communicable diseases. Both agencies charged with adoption of novel health technologies, and those developing public health policy, may be unaccustomed to dynamic modeling considerations (40-42). Knowledge translation and provision of educational opportunities and “short-courses” for professional development by modellers to decision makers will ensure that end users have the skills to understand these models. In addition to transparency of presentation, some authorities request access to the model itself. Where such disclosure is justified, measures should be put in place to protect modellers’ intellectual property.

Finally, it should be noted that in instances where several modeling groups have evaluated similar policy questions using disparate approaches, joint publication can help build confidence in the use of models as a tool for policy (see for example (43)).

Key considerations specific to the transparent presentation of communicable disease models include the provision of information on how “effective” contact rates and mixing patterns have been inferred, as estimates will depend both on the data used to derive rates, and the assumed model structure, such that different estimates may be obtained even using a common data set. For empirical, literature derived estimates (as in (44, 45)), there are large variations in the values of these estimates. Mixing behaviour should be clarified, for example by specifying the mixing matrix used.

When system dynamics models are used, the relevant system of differential equations should be written out and included as a supplement or appendix to the original analysis. When agent-based models are used it may be necessary to specify the behaviour of agents in greater detail. This will include factors such as movement of agents and mixing assumptions. Descriptions of movement should address whether the model makes use of geographic zones, how those zones are defined, and how agents move between zones. Descriptions of mixing behaviour should include how new contacts are acquired, as well as the length of time that partnerships last (if relevant).
When is it Appropriate to Use a Dynamic Transmission Model?

Recommendation:

A dynamic model is needed when a modeller is trying to evaluate an intervention against an infectious disease that 1) has an impact on disease transmission in the population of interest, and/or 2) alters the frequency distribution of strains (e.g., genotypes or serotypes).

Rationale

Static models (models without interaction) can be used 1) if the intervention is unlikely to change the force of infection (the per susceptible risk of infection) or, 2) to estimate the worst-case scenario when herd immunity or age shifts due to changing force of infection cannot produce negative effects. Static models cannot adequately take into account herd immunity effects nor shifts in the age distribution of infection induced by interventions. Risk of infection in susceptible individuals, so-called “force of infection” is constant in time in static models, while in a dynamic model it is a function of the proportion of the population that is infected (which changes over time). Hence, when the force of infection is unlikely to change following an intervention (i.e. herd immunity effects are unlikely to occur) then static models can adequately predict effectiveness. If intervention uptake is very low (e.g., low vaccine coverage) or is targeted at groups that do not have an impact on overall transmission then static and dynamic models produce similar results (1, 46).

Furthermore, results are also similar for vaccines or interventions that do not prevent the circulation of the pathogen since herd immunity effects are negligible.

Dynamic transmission models should be used if an intervention is likely to change the force of infection. This can occur in several ways. An intervention may decrease the proportion of the population that is susceptible (e.g., mass vaccination), the contact rates between individuals (e.g., closing schools during a pandemic), duration of infectiousness (e.g., antivirals), and/or the probability of transmission per act (e.g., antiretrovirals). By taking into account the changes in the force of infection following an intervention, dynamic models can 1) produce non-linear dynamics, 2) predict a higher number of cases prevented and 3) predict either increases or decreases in morbidity and mortality due to shifts in the age at infections. Note that using static models does not always produce conservative results. For example, the use of static models may overestimate the effectiveness of mass vaccination at preventing serious disease since they cannot capture possible increases in morbidity due to shifts in the age at infection (1), such as those that occurred after rubella vaccination in Greece (24).

Some diseases are caused by several types or subtypes of pathogens, and interventions can induce selective pressures that cause a subset of these types or even other microbes to gain a competitive advantage (10, 47). Examples are type replacement following pneumococcal and Haemophilus influenzae B conjugate vaccination (10, 48, 49) and antimicrobial-resistance (47, 50). Dynamic transmission models are necessary in such instances.

Finally, decision makers are often interested in local or national elimination of an infectious disease, or eradication (i.e., global elimination of the disease). The ability to eliminate a disease is a feature of communicable
diseases, as the non-linear (herd) effects mean that it is possible to eliminate without reaching everyone in the population. Since no intervention can ever target everyone (some will always refuse, or not be reached), and no intervention is ever 100% efficacious, elimination is not achievable in a static modelling framework. Dynamic models must be used if elimination is a goal.

Several schemata exist for guiding the decision to use of dynamic or static models (2, 15, 46), and a number of well-written papers demonstrate the divergence in predictions between static and dynamic models (1, 2, 16, 51).

What Type of Model to Use?

Recommendation:

The appropriate type of dynamic transmission model should be used for the analysis in question, based in part on the complexity of the interactions as well as the size of the population of interest 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.

Rationale

There are several different types of models that can be utilized to simulate the dynamics of communicable diseases. Broadly these can be classed as deterministic or stochastic, and population-based (sometimes known as compartmental) or agent- or individual- (agent-) based models.

In deterministic models every state variable is uniquely determined by the parameter values and the previous values of the state variables. Thus deterministic models will always give the same results if the model is run with the same starting conditions and parameter values. The state variables in a stochastic model are not described by unique values, but by probability distributions. That is, stochastic models inherently incorporate the role of chance in determining the state of the system. This often occurs in small populations, or when one of the subgroups in a model is small (such as at the beginning or end of an epidemic), when local extinction is likely. In these circumstances stochastic models are usually more appropriate. Deterministic models approximate the average behaviour of a system and are most appropriate when all population subgroups in the model are large. They are comparatively easy to fit to data and may be easier to calibrate.

Population-based models track groups of individuals (e.g. they simulate how the number of infectious or susceptible individuals changes over time). An alternative method is to model each individual, in an individual- (or agent-) based model. Here, the status of each individual is explicitly tracked over time. These models treat individuals as discrete entities who do not move between “compartments” but rather change their internal “state” (e.g., susceptible, infected, etc.) based on their interactions. As one of the characteristics attached to an individual is prior history (e.g., number of prior infections), they are particularly useful when risk depends on past events; representation of such phenomena in compartmental models requires large numbers of compartments. Furthermore, individual-based models can incorporate population heterogeneity relatively easily, and also have the flexibility to assess complex
interventions. Disadvantages include slow speed, lack of analytical tractability and challenges in parameterization. They
are invariably stochastic in nature. Compartmental (population-based) models can be either stochastic or deterministic.

Methodological Uncertainty

Recommendation:

Conduct sensitivity analysis on the time horizon and discount rate.

Rationale

Although many guidelines for economic evaluation specify the use of a “lifetime” time horizon, the concept of
a lifetime horizon is not well defined for dynamic transmission models, as these often concern whole populations,
which change over time due to births, deaths and migrations. An infinite time horizon could capture all of these effects,
but is clearly impractical. Fixed time horizons can produce artefacts; for example, if a cohort is vaccinated just before
the end of the time horizon the benefits to these individuals will not be included in the cost-effectiveness estimate,
though the costs of vaccinating them will. Other benefits and negative outcomes may vary non-monotonically over
time (i.e., may not strictly increase or decrease), making projections of economic attractiveness dependent on the time
horizon chosen (46).

For high discount rates the issue of time horizon may become less important, as distant future costs, savings
and health gains add little to the total. In the absence of discounting results may intimately depend on the time
horizon. Thus, it is recommended that modellers conduct sensitivity analysis on both the length of the time horizon
and the discount rate (2, 46, 52).

Structural Uncertainty

Recommendation:

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

Rationale

Structural uncertainty refers to the impact of model choice and structure on projections of cost and effect,
(and thus potential policy decisions). Structural uncertainty may relate to transmission routes and important risk
groups (by age, gender, or risk status), behavioural assumptions about contact patterns (e.g. instantaneous
partnerships versus long-term partnerships, the nature of mixing between age groups, etc.), the durability of immunity
following infection, changes in infectiousness of hosts over time, and strain competition and replacement in the
pathogen. A decision not to include a specific variable or structure in the model may also have consequences for the
results obtained. Structural uncertainty is often ignored in model-based economic evaluations, despite evidence that it
can have a much greater impact on results than parameter uncertainty (1, 2, 31, 51).
Often not enough is known about the biological properties of a system for precise definition of functional relationships; alternately, there may be several possible approaches to derive a model framework for a specific biological process. Structural uncertainty can be extremely influential in dynamic models due to non-linear feedback effects leading to qualitatively different dynamic regimes (33, 34, 51). It is particularly important, therefore to give due consideration to this aspect when reporting the results of an infectious disease model.

When interventions are incorporated into models, choices must be made regarding the structure of implementation in the model. For vaccine programs, key areas of structural uncertainty may relate to the representation of actual timing of vaccine doses and the impact of boosting; several components of vaccine effectiveness may be difficult to distinguish from empirical data; for example it may be difficult to distinguish vaccine “take” (the probability that a vaccinated individual develops measurable immunity) from vaccine efficacy (the degree of protection against infection per contact). Models of sexually transmitted infections often pose challenges related to explicit structural representations of partnerships (and partner concurrency), contact tracing or partner notification, and reinfection within partnerships (53).

Sensitivity analysis and Interpretation

Recommendation:

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

Rationale

One function of a sensitivity analysis is to give some indication of the degree of influence a change in parameter values may have on the outcome of interest. In non-linear dynamic transmission models the existence of regions of parameter space that characterise distinct types of model behaviour (e.g., epidemic spread vs. extinction) complicates such analyses. It is helpful if modellers define such behaviourally distinct regions of parameter space and explicitly state whether or not the sensitivity analysis has been confined to one region or not. 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.

Numerical Techniques

Recommendation:

For differential equation-based models, adaptive time step methods for numerical integration, that allow the degree of error tolerance to be specified in advance, are preferred to those that use a fixed time step of indeterminate accuracy.

Rationale

In general, the systems of differential equations commonly used in dynamic transmission models cannot be solved analytically. Thus, numerical integration techniques are used to approximate these systems. Such approximations
invariably result in error, but the magnitude of error can and must be controlled. This may be achieved by the use of adaptive time step methods. If a fixed time step methodology is used that utilises too large a step, then this error may be sufficiently large to influence the results of the model. By contrast, the use of very small time step to avoid such error may lead to a slow and inefficient model.

Reporting 1: Transparency

Recommendation:

If using a differential equations model, provide the model equations. Tabulate all initial value and parameters, including the mixing matrix and supply details of the type of mixing considered.

Rationale

Showing the model equations and details is required to ensure transparency and reproducibility.

Recommendation:

If using an agent-based model, thoroughly describe the rules governing the agents, the input parameter values, initial conditions and all sub-models.

Rationale

Describing the rules that govern the behaviour of agents, parameter values, initial conditions and sub-models is required to ensure transparency and reproducibility. In particular, describing the rules surrounding the creation and dissolution of partnerships in models of sexually transmitted infections will help ensure face validity.

Reporting 2: Epidemic Outcomes

Recommendation:

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

Rationale

Dynamic transmission models are recommended to evaluate interventions that may have an impact on disease transmission or interventions that may result in changes in the frequency distribution of strains. Thus, all associated outcomes should be reported to optimize comparability of model results, as well as transparency. This information may also be of use to decision makers (54).


