The use of mathematical modelling studies for evidence synthesis and guideline development: a glossary

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Abstract

Mathematical modelling studies are increasingly recognised as an important tool for evidence synthesis and to inform clinical and public health decision-making, particularly when data from systematic reviews of primary studies do not adequately answer a research question. However, systematic reviewers and guideline developers may struggle with using the results of modelling studies, due at least in part to the lack of a common understanding of concepts and terminology between evidence synthesis experts and mathematical modellers. The use of a common terminology for modelling studies across different clinical and epidemiological research fields that span infectious and non-communicable diseases will help systematic reviewers and guideline developers with the understanding, characterisation, comparison and

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use of mathematical modelling studies. This glossary explains key terms used in mathematical modelling studies that are particularly salient to evidence synthesis and knowledge translation in clinical medicine and public health.

Keywords: Mathematical modelling studies; evidence synthesis; knowledge translation; guidelines; glossary

1. Introduction

Mathematical models are increasingly used to aid decision making in public health and clinical medicine.[1,2] The results of mathematical modelling studies can provide evidence when a systematic review of primary studies does not identify sufficient studies to draw conclusions or to support a recommendation in a guideline, or when the studies that are identified do not apply to the specific populations of interest or do not provide data on long term follow up or on relevant outcomes. For example, mathematical models have been used to inform guideline recommendations about tuberculosis (TB) control in health care facilities,[3] blood donor suitability with regard to human T-cell leukaemia virus type I (HTLV-I) infection,[4] and cancer screening.[5,6] Mathematical modelling studies are frequently used to synthesize evidence from multiple data sources to address a clinical or public health question not directly addressed by a primary study. For example, a mathematical model was used to synthesise evidence obtained from virological, clinical, epidemiological and behavioural data to help determine optimal target populations for influenza vaccination programmes.[7] Other examples are mathematical modelling studies that aim to predict the real-world drug effectiveness from randomised controlled trial (RCT) efficacy data (reviewed in Panayidou *et al.*[7]).

The development of methods for incorporating mathematical modelling studies into evidence syntheses and clinical and public health guidelines is still at an early stage. Systematic reviewers and guideline developers struggle with questions about whether and how to include the results of mathematical modelling studies into a body of evidence. The review of mathematical modelling studies predicting drug-effectiveness from RCT data identified twelve studies using four different modelling approaches.[7] Due to the varying use of key terminology between studies, and because certain terms can have different meanings in the literature, it was necessary to describe in the review each modelling approach in detail to

illustrate the differences between them. This effort highlights an important reason for the challenges in summarising the results of mathematical modelling studies. Researchers who develop and analyse mathematical models have different theoretical and practical backgrounds from systematic reviewers, guideline developers and policy-makers, which can result in a lack of a common understanding of concepts and terminology. These communication issues might result either in not using the findings of mathematical modelling studies in evidence synthesis and to inform decision-making, or accepting these findings without critical assessment.[8] A glossary of commonly used terms in mathematical modelling studies that are relevant to evidence synthesis and to clinical and public health guideline development could improve the use of such studies.

A mathematical model is a "mathematical framework representing variables and their interrelationships to describe observed phenomena or predict future events."[9] We define a mathematical modelling study as a study that uses mathematical modelling to address specific research questions, for example the impact of interventions in health care facilities to reduce nosocomial transmission of TB.[10] For the modelling studies that are most relevant to evidence synthesis and clinical and public health decision-making, the framework of the mathematical model represents interrelationships among exposure risks, interventions, health outcomes and health costs (all of these are *variables*) where their interrelationships are typically described by the *parameters* of interest. Mathematical modellers can use different methods to specify these *parameters*; they can use theoretical values, values reported in the scientific literature, or estimate the parameters from data using methods from statistical modelling. There is some overlap between the terms 'mathematical model' and 'statistical model' and their uses. Contemporary mathematical modelling studies increasingly include one or more statistical modelling parts. In this glossary, we will consider statistical models as a class of mathematical models that are often integrated into complex mathematical modelling studies to relate the model output to data through a statistical framework.

The goal of this glossary is to provide a common terminology for public health specialists who would like to incorporate the results of mathematical modelling studies in systematic reviews and in the development of guidelines. To identify the terms included in this glossary, we first made an exhaustive list of terms related to mathematical models. Terms were then selected based on discussions among experts attending the World Health Organization (WHO)'s Consultation on the development of guidance on how to incorporate the results of

modelling in WHO guidelines (Geneva, Switzerland, 26 April 2016). Experts included epidemiologists, statisticians, mathematical modellers, and public health specialists. The glossary is divided into three sections. In section 2, we define some key terms that can be used to characterise the scope of and approach to mathematical models, using examples from the field of infectious disease modelling. In section 3, we present a list of terms that are commonly used across different research fields in epidemiology to describe more detailed technical properties and aspects of mathematical models. In section 4, we first discuss how knowledge of the terms can help to assess whether a mathematical modelling study is appropriate for providing evidence for a specific question. We then use the example of the World Health Organization (WHO) guidelines for TB control in health care facilities[3] to show how mathematical modelling studies can inform recommendations. For more specific definitions of terms that are primarily used in infectious disease modelling, we refer to the glossary by Mishra et al.[11] Terms appearing in italics are defined in other entries of the glossary.

2. Terms used to define the scope of, and approaches to mathematical models

Before one starts to assess and compare the results of different mathematical modelling studies with each other, it can be helpful to fit them into a larger picture. Experts in systematic reviews and guideline developers need to be able to sort out which modelling studies are likely to help them draw a conclusion, formulate a recommendation, interpret the findings of another study, or understand the clinical or pathological background to a problem. Mathematical modelling studies can be characterised using several dichotomies that help to describe broad aspects, such as the scope and approach. Table 1 provides a list of some important model dichotomies, together with a brief definition, an example and their relevance to systematic reviews and guideline development.

A fundamental distinction can be made between *mechanistic* and *phenomenological models*. *Mechanistic models* use mathematical terms to describe the real-world interactions among different model variables. The parameters governing these models typically have a physical, biological or behavioural interpretation. Infectious disease models, for example, can describe the movement of individuals within hospital wards, and how infections are transmitted upon physical contact between a susceptible and an infected person.[10] These models have the advantage that specific interventions, such as infection prevention through quarantine or isolation, can be explicitly implemented. *Phenomenological models*, on the other hand,

describe the relationships among different model variables, consistent with fundamental theory, but not derived from first principles. Hence, this type of model does not attempt to describe or explain why and how certain model variables interact, but instead focuses on the functional relationship that best describes an observed phenomenon. Statistical models, such as regression models, are typically phenomenological and describe the statistical relationship or association between different model variables.

A *predictive model* can forecast future events, such as the course of an epidemic in a given population under different scenarios, whereas a *descriptive model* describes and/or explains previously observed phenomena, such as the effectiveness of past interventions. *Quantitative models* provide a numerical estimation of an intervention effect on model *variables*, and therefore depend on high-quality data to inform the model *parameters*. *Qualitative models* are usually relatively simple models that only provide insights into the direction of an effect, but not its precise magnitude. Nevertheless, they can be used to thoroughly investigate the interrelationships between model *variables* and the influence of specific *parameters* on health outcomes (also see *Analytic solution*). *Qualitative models* can also be useful to explore the potential for unintended consequences of interventions beyond the direct intended effects that might have been observed in RCTs. Finally, an important model dichotomy distinguishes between what drives the results of mathematical modelling studies. Most mathematical models incorporate a combination of some underlying theory, model assumptions and data. The results of a *theory-driven* model are primarily based on a priori knowledge or *assumptions* about specific interrelationships, such as the effectiveness of a particular intervention, and are not directly inferred from data. *Data-driven models* infer their results primarily from data, and are not driven by theory or *assumptions* that are not well supported.

3. Terms related to technical properties and aspects of mathematical models

3.1. Technical terms related to model development and structure

Once the mathematical modelling studies have been broadly characterised, and their purpose has been determined, it is important to gain a better understanding about some of the terms used to describe the technical aspects of the model used in a study. For example, has *heterogeneity* among different individuals been incorporated, or what simulation methods were used to obtain the model results? The following list includes some of the most frequently used terms in mathematical modelling studies in various fields of epidemiology.

The terms in Part 3.1 will help in assessing the technical aspects that relate to model development and structure. The terms in Part 3.2 are related to model calibration and validation.

Agent-based model See *Individual-based model.*

Analytic solution Relates the health outcomes directly to the model *parameters* using mathematical formulae. Models that can be solved analytically are usually simple models, while more *complex models* typically require a *computational (numerical) solution*.

Assumption In mathematical modelling studies, *assumptions* typically relate to the structure of the model and the supposed interrelationships of model *variables*. An important *assumption* in infectious disease models concerns the way in which individuals have contacts with each other. This could either be at random or involve some form of *heterogeneity*. In order to relate the model output to data via a statistical framework, one has to make additional assumptions about the way the data has been gathered and the expected random error.

Compartmental model This model type stratifies the population into different compartments, such as different health states. Compartments are assumed to represent homogeneous sub-populations within which the entities being modelled – such as individuals or patients – have the same characteristics, for example the same sex, age, risk of infection or death. The model can account for the transition of entities between compartments (see *State-transition model*).

Computational (numerical) solution This describes the approach of solving a mathematical model using either *deterministic* or *stochastic* (see *Monte Carlo methods*) simulation techniques to iteratively calculate the model *variables*, which are often time-dependent, for a specific set of *parameters*. Iteratively calculating the model *variables* means updating the population characteristics at each time point based on the simulated population characteristics at previous time points. *Computational solutions* are used when the model is too complicated for deriving an analytic solution.

Continuous-time model This is a *dynamic model* where time is treated as a continuous *variable* (in contrast to a *discrete-time model*), meaning that the state or value of all other *variables* (or health outcomes) can be calculated for any time point of interest.

Cycle length In a *discrete-time model*, *cycle length* represents the interval from one time point to the next, for example a specific number of days, weeks, months, or years.[7]

Decision analytic model This term refers to mathematical models that synthesise available evidence to estimate health outcomes and guide decision making. The term is typically used in health economic analyses.

Deterministic model This model type typically describes the average behaviour of a system (e.g., populations or sub-populations) without taking into account *stochastic* processes or chance events in single entities (e.g., individuals). Hence, such models are typically applied to situations with a large number of individuals where stochastic variation becomes less important and *heterogeneity* can be accounted for using various sub-populations. The *parameters* of a deterministic model are typically fixed, and a simulation always produces the same result. *Deterministic models* are typically easier to *calibrate* to data than *stochastic models*.[11,12]

Discrete-time model This type of *dynamic model* treats time as a discrete *variable* (in contrast to a *continuous-time model*) and other *variables* (or health outcomes) can only change at specific time points.[7]

Dynamic model A *dynamic model* contains at least one time-dependent variable.[11] This type of model is used to *describe* and *predict* the course of health outcomes (e.g., infection incidence) over time when, for example, the exposure risk (e.g., infection prevalence) also changes over time.

Heterogeneity In mathematical modeling studies, this typically describes the differences among individuals, or the variability across *parameter* values for a specific group of individuals, due to their demographic, biological or behavioural characteristics.

Individual-based model This is a *stochastic model* representing individuals as discrete entities with unique characteristics. An individual-based model can be useful to accommodate *heterogeneity* in a given population. Individual-based models are also often referred to as *agent-based* or *micro-simulation models*. Whilst individual-based models can provide more realistic representations of a system, they can be difficult to parameterise because they require much more detailed knowledge, or *assumptions*, of how *variables* interact. The

stochastic nature of these models makes them computationally intensive and challenging to *calibrate*.

Markov model A *Markov model* assumes that the future state of variables depends only on the current state, but not the previous states, of variables. For example, in a *discrete-time Markov model*, the number of new infected individuals is calculated based on the total number of infected individuals at the previous time step.

Micro-simulation model See *Individual-based model.*

Monte Carlo methods These are a class of *computational* methods that are based on random sampling. *Monte Carlo methods* are typically used to simulate *stochastic models* and are *computationally* intensive.

Ordinary differential equations Equations that describe the change of a dependent *variable* with respect to an independent *variable*, based on differential calculus. For example, *ordinary differential equations* can be used to describe the increase and decrease of infected individuals in *continuous* time resulting from acquisition or clearance of infection. *Ordinary differential equations* are typically used for *deterministic*, *compartmental models*.

Parameter A *parameter* is a quantity used to describe the interrelationships between model *variables*. For example, *parameters* can describe how long different individuals reside in different health states, or how likely they are to transmit a disease to another person. There are different methods to specify the value of *parameters*. Mathematical modellers can either choose theoretical values based on specific *assumptions*, or set the values based on literature reviews or model *calibration*.

Parsimonious model In a *parsimonious model*, *descriptive* or *predictive*, the number of *assumptions*, *parameters* and *variables* is minimised. *Parsimonious* models are often relatively simple, but they can also become more complex, if they achieve the right balance between complexity and explanatory power.

Population-based model A type of *deterministic or stochastic model* where individuals that share the same characteristics on average are being grouped into a single population or several sub-populations. In contrast, an *individual-based model* treats every individual as a single entity that can have unique characteristics.

State-transition model *State-transition models* assume that individuals can be in different (health) states and move (transition) between them.[13] They are typically described using the framework of either *Markov models* or *individual-based models*.

Static model In a *static model*, all *variables* are independent of time and constant. A *static model* typically describes the equilibrium of a system, and relates the model *variables* for a particular time point only. In contrast to *dynamic models*, this type of model cannot take into account time-dependent changes of exposure risks or health outcomes. Decision-tree models are *static models*.

Stochastic model A type of model where the *parameters*, *variables* and/or the change in *variables* can be described by probability distributions. This type of model can account for process variability by taking into account the random nature of variable interactions, or can accommodate *parameter* uncertainty, and so may predict a distribution of possible health outcomes. Considering process variability can be particularly important when populations are small or certain events are very rare. *Stochastic models* are often simulated using *Monte Carlo methods*.

Time horizon A *time horizon* denotes a chosen time at which point the effect of an intervention will be evaluated. The *time horizon* should reflect the health outcomes and the relevant intermediate and long-term effects of an intervention.[1]

Variable *Variables* describe model elements such as exposure risks, interventions or health outcomes that can vary between settings or over time. The value of a dependent *variable* (e.g., number of infected individuals) changes in relation to an independent *variable* (e.g., time).

3.2. Technical terms related to model calibration and validation

Calibration *Calibration* is the process of adjusting model *parameters* such that the model output is in agreement with the data that are used for model development.[14] The aim of *calibration* is to reduce *parameter uncertainty* in order to achieve high model *credibility*.

Credibility The *credibility* of a model refers to judgements about the degree to which the model provides trustworthy results. Several dimensions of *credibility* have been described, including *validity*, design, data analysis, reporting, interpretation and conflicts of interest.[15]

Sensitivity analysis A range of techniques used to test the impact of the *assumptions* made about the *parameters*. The analysis can be done by changing one *parameter* (one-way, univariate) or simultaneously changing several *parameters* (multi-way, multivariate). The *parameters* selected for sensitivity analyses are thought to have an impact on the outcome of interest. In a deterministic sensitivity analysis, a *parameter* is assigned a limited number of values, while in a probabilistic sensitivity analysis each *parameter* is assigned a probability distribution, and parameter values are randomly sampled from these distributions.[1,11]

Uncertainty analysis A range of techniques to determine the reliability of model results or predictions, accounting for uncertainty in model structure, input *parameters* and/or methods used for data analysis.[11] *Structural uncertainty* relates to the extent to which the structure of the model captures the key features of the system[16-18] and can be analysed by comparing the results of models with different structures. *Parameter uncertainty* stems from the model *parameters* that are used but whose true values are not known because of measurement error or an absence of evidence.[16,18] This uncertainty can be analysed by examining model outputs for a range of values of the parameter. *Methodological uncertainty* arises when there are different methods for analysing or expressing model outputs. This term is used mostly in health economic modelling.

Validation A term describing processes for assessing how well a model performs and how applicable the results are to a particular situation.[19] There are five main types of validation: *face validation* (subjective expert judgement about how well the model represents the problem it addresses); *internal validation (internal consistency, verification,* addresses whether or not the model behaves as intended and has been implemented correctly); *cross validation* (*convergent validity,* model results are confirmed by other models); *external validation* (model results predict outcomes obtained in a real world setting or in a dataset different from the one used for model development); *predictive validation* (model-predicted events are later corroborated by real-world observations).[7,20]

4. Mathematical modelling studies in guideline development

In addition to providing a useful common terminology for public health specialists and mathematical modellers, the description of different model types and other terms defined in the glossary facilitate interpretation of the results of mathematical modelling studies and inform their incorporation into the guideline development process. As a first step, one needs to identify whether a particular research question, e.g., the evaluation of public health programmes, long-term effectiveness or comparative effectiveness, can be investigated using a model. Next, it will be necessary to assess whether existing mathematical modelling studies are appropriate to inform or support a research question or recommendation. We identified four comprehensive frameworks of good modelling practice.[21] These frameworks cover items such as relevance, conceptualisation of the problem or model structure. Questions such as whether the model population is relevant, the *variables* represent the desired health outcomes, the necessary *heterogeneity* is taken into consideration, the *time horizon* is appropriate, or the *assumptions* are justified can help in the assessment of mathematical modelling studies. Other items concern *validity* or *consistency*, i.e., the performance of the model according to its specifications. The model should also consider *uncertainty* with regard to the structure, *parameters* and methods. Finally, *credibility*, which takes a number of these items into account, can then be used as the central concept for guideline developers to address the appropriateness of a mathematical modelling study for providing evidence for a specific question,[22] as illustrated in the following example.

Prevention of TB transmission in hospitals, and particularly of multidrug-resistant TB, is essential in all countries and requires a combination of strategies. Predicting the spread of TB in a hospital and the surrounding community, and how alternative methods of control might limit the emergence of resistance, are complex non-linear processes. It is, however, ethically and logistically impossible to conduct RCTs to examine the efficacy of these strategies. Mathematical modelling studies that use observational evidence can therefore play an important role in deciding which strategies are likely to be the most effective. The WHO guideline development group for TB infection control in health-care facilities, congregate settings and households assessed systematic reviews of the evidence, which included mathematical modelling studies.[3]

One mathematical modelling study that the guideline committee considered investigated the effects of several different control measures on the spread of extensively drug resistant

(XDR) TB in a community in South Africa.[10] The model described the transmission of TB in a complex system that included *variables* representing or contributing to: both a hospital and the surrounding community; different TB health states such as susceptible, latent, infectious and recovered; drug resistance; HIV infection; and the effects of different control interventions alone and in combination. Hence, the study considered the transmission setting that was of relevance to the guideline and the model structure included the desired health outcomes and *variables*. The authors used a *mechanistic* approach to make explicit the way in which stages in the transmission and natural history of TB are related. A *deterministic*, *compartmental model*, using *ordinary differential equations* to describe the transitions between different health states in a *dynamic* way was appropriate because it allowed the right balance between complexity and tractability. Key *parameters* that described the natural history, such as rate of natural clearance and rate of relapse were based on the literature and their influence was assessed in an *uncertainty* analysis. *Parameters* such as the transmissibility coefficient were calibrated using longitudinal data of individuals in a South African community, where data on TB were collected. The model outputs provided *quantitative* predictions about the percentage reduction in XDR-TB cases over a reasonable *time horizon*. *External validation* of the model was performed using cross-sectional data with information on the prevalence of TB and of drug resistance and the proportion of resistance cases in people with HIV infection. In summary, the mathematical modelling study covered many of the critical items and we would conclude that the study has a high credibility.

Compared to natural ventilation, the authors found that mechanical ventilation alone would reduce XDR-TB cases by 12% (range 10-25%). The use of respiratory masks by health workers would prevent 2% of all TB cases, but nearly two-thirds of XDR cases in hospital staff. The guideline development group considered this study together with other observational and modelling studies identified through the systematic review. Even though the summarised evidence for the use of ventilation systems and particulate respirators was weak, indirect and of low quality, the studies suggested that these interventions are favourable for TB infection control.

Conflicts of interest

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Table 1. Model dichotomies describing the scope of, and approaches to, mathematical models in infectious disease epidemiology.

Model dichotomy*	**Brief definition**	**Example**	**Potential relevance or use for systematic review or guideline development**
Mechanistic *vs.* Phenomenological	Uses mathematical terms to explicitly describe the mechanisms of infection transmission, pathogenesis and control measures. Uses mathematical terms to describe the interrelationships between risks and outcomes without making *assumptions* about the underlying mechanisms.	*Compartmental model* that describes the transmission of influenza and the effects of vaccination in England and Wales.[23] Estimation and Projection Package (EPP) that fits a simple epidemic curve to HIV surveillance data.[24]	Allows implementation and modelling of different vaccination scenarios, such as targeting children or elderly. Cannot be used to describe intervention effects in detail, so it is less likely to investigate hypothetical scenarios or interventions.
Predictive *vs.* Descriptive	Forecasts future events. Describes and/or explains previously observed phenomena.	Impact projections of malaria vaccine for timeframes longer than previously conducted trials.[25] Quantifying the effect of malaria disease control efforts in Africa between 2000 and 2015.[2326]	To investigate the expected future impact of implementing or changing interventions, and to set new targets. To assess the effectiveness of past interventions or explain previous events and learn from them.
Quantitative *vs.* Qualitative	Provides a precise numerical estimation or the expected range of an effect. Describes the direction or general size of an effect.	HIV prevalence after expanding access to antiretroviral therapy.[15] Increasing herpes zoster incidence after mass childhood vaccination against varicella.[27]	To obtain estimates of an effect that can be incorporated into economic (cost-effectiveness) analyses. Could indicate how and under what conditions an intervention could cause a specific epidemiological outcome. Might influence conditions of a recommendation.
Theory-driven *vs.* Data-driven	Results are driven by theory/*assumptions* Results are inferred	Investigating the theoretical strategy of universal testing and immediate treatment for HIV.[28] Influenza transmission	Can provide a rationale for considering a particular intervention. In the absence of data, results need to be critically evaluated in light of modelling *assumptions*. Can be used to assess

	from data	model to estimate the effectiveness of historical vaccination programmes.[23]	effectiveness of interventions where randomised controlled trials are not possible. Evidence primarily relies on the quality of the primary data.

* Some of these dichotomies are adapted from Bolker, 2008.[29]

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