A User's Guide to Infectious Disease Modelling

EDITORS:
Jodie McVernon[1] and James Wood[2]

CONTRIBUTORS:
Patricia Campbell[1], Nicholas Geard[1], Kathryn Glass[3], Emma McBryde[4], James McCaw[1], Jodie McVernon[1], Robert Moss[1], Joshua Ross[5] & James Wood[2]

PRISM²

1. The University of Melbourne
2. UNSW Australia
3. Australian National University
4. James Cook University Australia
5. The University of Adelaide

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About this guide

This guide is intended as an introduction to interpreting the results of mathematical modelling studies in epidemiology. Such studies are increasingly used to support decision-making related to immunisation policy and the control of vaccine preventable diseases. The guide is designed to be read either in full or on a section by section basis, with these sections closely relating to the ordering of material in published modelling papers. Where it has been essential to use more technical terms to convey a precise message, these have been *italicized* to indicate inclusion in the attached glossary found on pages 24-26 of this document.

The guidance has been kept fairly general as we could not cover the large variety of specific details that appear in the literature. References for further reading are provided at the end of the document.

Introduction to mathematical models

What is a mathematical model?

Dynamic mathematical models of infection aim to represent in a simplified manner the many processes and determinants involved in the *acquisition*, experience and ongoing spread of disease. The basic '*SIR*' model (Figure 1) uses a series of *ordinary differential equations* to characterize *epidemic* behaviour through the transition of individuals between the susceptible (*S*) *state* and that of being infected and infectious (*I*). These events are not independent of each other, as the prevalence of infectious individuals (*I*) directly influences infection risk (in conjunction with the intrinsic 'infectiousness' of the specific pathogen in the population), represented here by β, which determines the rate of movement from *S* to *I* as shown in Figure 1. Once recovered (*R*), individuals are immune and no longer susceptible to infection, and collectively contribute to the resolution of an outbreak through increasing *herd immunity*. While simple in construction, such models and extensions have yielded helpful insights of relevance to infectious disease control over the past century.

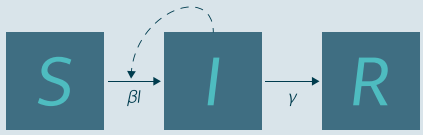


Figure 1: *The SIR model paradigm. Here γ represents the rate of recovery (1/duration of infection), while the dependence of infection risk on prevalence is indicated by the dashed curve.*

The basic reproduction number (R_0)

In a fully *susceptible* population, the number of secondary cases produced by a single introduced case can be calculated as β x *S* x the duration of infectiousness, a useful *epidemic* descriptor termed the *basic reproduction number* (R_0). The basic reproduction number can be used directly to define the quantity known as the *critical immunization threshold*, or the proportion of the population that needs to be immunized to eliminate an infectious disease. For an infectious disease to spread in a population, infectious individuals must on average produce at least one secondary case, ie $R_0 \geq 1$. The variety between vaccine preventable diseases in terms of their infectiousness and the difficulty achieving elimination through vaccination is indicated Table 1.

Table 1: *Approximate R_0 values[a] and critical immunisation thresholds for common vaccine preventable diseases*

Disease	Basic reproduction number (R_0)	Critical Immunization threshold
Chickenpox	7 – 12	86-92%
Measles	11 – 18	91-94%
Mumps	7 – 14	86-93%
Pertussis	10 – 18	90-94%
Polio	5 – 7	80-86%
Rubella	6 – 12	83-92%
Smallpox	3 – 7	67-86%

[a]These values are primarily taken from ranges shown in Anderson and May (1991) for developed settings, with the smallpox range taken from House et. al. (2010). It should be noted that these are indicative only, with a wide variety of estimates published for each of these disease in more recent literature depending on model design and setting.

The critical immunization threshold for elimination

The critical immunization threshold (P_c) and R_0 are related to each other through the following formula:

$$P_c = 1 - \frac{1}{R_0}$$

If, for example, each infected individual will on average infect 20 others (R_0=20), then more than 19 of those 20 people need to be effectively vaccinated to ensure that an average of less than 1 contracts the disease (ie vaccine coverage of >95%). On the other hand, if on average only 2 people will be infected (R_0=2), effective immunization of just over 1 out of every 2 individuals would be sufficient for disease elimination (ie effective vaccine coverage of >50%).

These estimates are useful 'ball park' indicators, but make simplifying assumptions: for instance they assume that all individuals in the population are equally susceptible and infectious and don't take into account epidemiological risk factors such as age. For instance calculations for a sexually transmitted infection such as human papilloma virus would need to take into account differences in sexual activity by age and gender with further stratification by partner numbers likely required. More significantly, it assumes that vaccines are 100% protective and that protection is life-long. In practice, infectious diseases and the vaccines designed to prevent them usually differ from these assumptions to a greater or lesser degree.

Uses of modelling relevant to immunization and vaccine preventable disease control

In this document we focus on two major uses for mathematical modelling in relation to vaccine-preventable diseases.

1. *Prediction to support decision making in the face of uncertainty.*
   Examples of this use include predicting the likely *impact* of an emerging infectious disease, or anticipating likely changes in disease burden following application of a new or altered immunization program. Increasingly, infectious disease models also form the basis of *cost-effectiveness evaluations* for vaccines and we provide some guidance in relation to the economic component of such evaluations.

2. *Enhance understanding of infectious disease epidemiology.*
   Examples of this may include applying novel methods to analyse disease surveillance data, and examining past trends in disease to more accurately characterise important disease processes or investigate impacts of past interventions.

Such models frequently draw on many sources of information, ranging from basic biology, through to clinical trials and observational studies, as well as studies of human interactions and behaviour – all of which are relevant to understanding different aspects of infection spread.

Key references

Anderson R and May R. (1992). Infectious Diseases of Humans. OUP Oxford.
Key early book that describes the details of models and relevant data with a strong focus on vaccine preventable diseases in the first half of the book.

Delva W, Wilson DP, Abu-Raddad L et. al. (2012) HIV Treatment as Prevention: Principles of Good HIV Epidemiology Modelling for Public Health Decision-Making in All Modes of Prevention and Evaluation. PLoS Med 9(7): e1001239.
A set of guidelines with a similar focus to these on the application of infectious disease models in the context of HIV.

Husereau D, Drummond M, Petrou S, et. al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ 2013 346:f1049
The checklist included here is loosely based on the one provided as part of the CHEERS statement presented in this paper.

Vynnycky E and White R (2010). An introduction to Infectious Disease Modelling. OUP Oxford.
Adapted from an intensive 2-week course taught at the London School of Hygiene and Tropical Medicine, this is an introductory book aimed at readers without a strong mathematics background.

Guidelines

Within the next few sections we provide background information and a guide as to what should be expected and what to look for when reading and interpreting modelling papers in relation to immunisation policy. The structure closely follows that of published papers and in addition each section contains a content summary for quick reference.

AIMS
Purpose, scope and relevance to policy

Key points

- The main purpose of models is often to capture dynamic effects of transmission and interventions that are difficult to measure in clinical trials.
- Models are suited to purpose – for some questions a very simple model will suffice, while in other situations more complexity will be required.
- Look for discussion of points of difference between the model being used and those adopted in previous research on the topic.
- Look for discussion of generalizability. Basic biological parameters are often transferrable but population characteristics including surveillance data, health outcomes and costs may not be.
- Readers should consider the feasibility of proposed interventions and assess whether modelled outcomes can be compared with routinely collected data.

Purpose and rationale for model development

As with any scientific study, the use of mathematical modelling methods to answer a particular question needs to be justified. Ideally a clear rationale for the use of modelling should be provided. Typically this rationale will relate to the need to synthesise evidence from a variety of sources or to investigate the consequences of new developments such as vaccines or emerging infections. In particular the ability to calculate *herd immunity* effects, whereby introduction of a vaccine programme leads to a reduction in disease in unimmunized individuals or non-targeted age groups, are often not available from empirical studies such as clinical trials. Models that explicitly represent *transmission* of infection between and among immunized and unimmunized individuals can estimate or predict these effects for new interventions. This ability to capture herd immunity effects is also important when attempting to estimate key epidemiologic quantities (e.g. *duration of immunity* or the *reproduction number*) as such estimates are often confounded by dynamic changes in disease epidemiology.

A more detailed consideration of the rationale also should involve a discussion of what the appropriate model type and structure is. This will be covered in more detail below but for example this might relate to the set of health states that adequately describe the natural history of disease but also differences within populations such as age or gender. Here the level of detail is likely to vary based on the available data, findings from prior work on the subject and pragmatic decisions around what elements are relevant to include. Ideally a model should be as simple as possible, provided that it contains all the important details (this principle is guided by *Occam's razor* and sometimes referred to as parsimony) but this is easier said than done! However, depending on the question being considered certainly great variation in levels of detail can be expected. For instance if a novel strain of influenza emerged in another country there would be interest in determining how quickly it might arrive in Australia. A simple SIR-type model would likely give a reasonable answer to this question in a short amount of time.

Consider, however, the provision of human papilloma virus immunisation to boys in Australia. Here impacts on both men and women over a considerable time-frame are of interest. We also know that infection risks vary markedly by age and between population subgroups. Here, the high degree of heterogeneity in the rate of sexual contacts would need to be accounted for to avoid erroneous conclusions being drawn from the model. Therefore the appropriateness of the model should be discussed in relation to the complexity of the question being addressed. The downside of this from a reader's point of view is that unlike most statistical analysis, there is wide variation in assumptions and model structures used even in relation to the same research question. Therefore it's important for modelling studies to be contextualized in relation to earlier models, with points of difference clearly articulated. In general modelling approaches evolve over time to include more detail as the evidence base to inform them increases, and limitations of previous models become apparent.

Scope and generalisability

It's worth recognizing that while many modelling studies of vaccine preventable diseases do have direct relevance to policy, others are also created for more theoretical or scientific purposes. For instance, models that do not stratify by age are probably not relevant to assessment of effects of a new vaccine, although insights from such models might ultimately develop into practical approaches to disease control.

As a reader you are hoping to see a clear description of the purpose of the study, that takes into account the setting and scenarios of interest and the potential for generalisation. Very theoretical studies may demonstrate mechanisms of infection and immunity that are broadly generalizable, but the way these play out for disease control in specific contexts can vary. Vaccine effectiveness or cost-effectiveness studies are more likely to incorporate local data on disease burden, and consider feasible control strategies, but care needs to be taken in application to other contexts. For instance, the observed 'real world' impacts of childhood pneumococcal vaccine programs in different high-income settings have varied both in absolute and relative terms. Similarly, it would not be reasonable to directly transfer results from a model based on the United States' population to a European country. That said, one particularly useful application of models is to shed light on the reasons why the same intervention may lead to different population level outcomes for clinical disease burden between countries and risk groups.

Relevance to policy

Ideally modelling papers make the policy relevance very clear. Typically for instance, effectiveness and cost-effectiveness evaluations undertaken by agencies such as Public Health England have a very clear and direct relationship to immunisation policy. The models are expressly commissioned for this purpose, and developed collaboratively using the close links between modellers and policy makers in that setting. Relevance to policy includes discussion of the feasibility of proposed interventions and whether the outcomes being evaluated are measurable through surveillance and are of clinical or public health importance. For instance, many *endemic* infectious diseases spread primarily through mild or asymptomatic infection, but primarily cause serious invasive disease in certain age or risk groups – does the model consider and differentiate the impact of interventions on infection as opposed to severe disease?

METHODS
Modelling approach and description

Key points

- There are fundamental differences between types of models, in particular between deterministic and stochastic models. The former are best suited to interventions in large populations, while the latter capture chance events and are more useful in small population and outbreak situations.
- Deterministic, compartmental models are most commonly applied in immunisation but there is growing use of stochastic models with some degree of individual-level variability. These are typically referred to as agent-based or individual-based models.
- Infectious disease models typically include whole populations (not just cohorts) and include some level of demographic detail (heterogeneity), with age the most commonly used variable used to stratify the population. Inclusion of births and deaths is typically required to capture disease epidemiology over decadal or longer time-frames.

Deterministic and stochastic models

Mathematical models, as described earlier, represent the movement of individuals in the population between disease states. One important classification of these models is whether they are *deterministic* or *stochastic*.

In a *deterministic* model, there is a pre-determined relationship between the model structure and inputs and the model outputs: the model will always provide precisely the same set of outputs if the inputs and structure are kept the same. So if the initial *S*, *I* and *R* values are left unchanged, and the transmission rate and duration of infection are the same, the model will return the same solutions each time it is implemented. A *stochastic* model, on the other hand, can produce different model outputs for the same model structure and inputs. Hence, it attempts to account for the variation that arises from unspecified and natural sources. Instead of pre-determined movements between states, a *stochastic* model samples from the range of possible outcomes (represented by pre-defined *probability distributions*). In the above example, even if the initial values for the *S, I, R* remain unchanged, a *stochastic* model will allow the number of infectious contacts and duration of infection to vary between individuals according to the chosen probability distributions.

How does one decide on which approach is more appropriate? Well, deterministic models emphasize average effects and work best in large populations, where infection risks are fairly homogenous. Deterministic models are simpler to solve numerically, and are often efficient and valid representations of common *endemic* or established *epidemic* infectious diseases, including most vaccine preventable diseases.

However, when population sizes are smaller or infection is rare, *stochastic* models become appropriate. This is because individual differences play a much greater role in what may happen when there are only a small number of cases. For instance with a newly emerged infectious disease, it is entirely possible that an imported case will lead to no secondary infections because of for instance limited contact with other people. Similarly, for a disease such as measles that is in an elimination phase imported cases in general do not lead to large outbreaks. This phenomenon, known as *fade-out*, can be captured by *stochastic* models, because they allow a range of probabilities that ongoing infection spread will occur, including the possibility of failure. This behaviour does not occur in deterministic models, which will always produce an epidemic provided the reproduction number is greater than 1.

Why not always use stochastic models? In comparison to deterministic models, stochastic models are slow to run (particularly in large populations) and need to be run many times (usually 1000s of times) to investigate a single scenario with fixed parameters. This also raises challenges with presentation of findings, particularly if other forms of uncertainty need to be accounted for.

Compartmental and individual-based models

Another important classification is the approach to representing the population. *Compartmental*, or *state-based* models group individuals in the population into states based on characteristics relevant to the infectious process (*S*, *I* and *R*), often *stratified* to include individual risk determinants such as vaccination status or age. These models are quick to develop, and work best when infection risks are more uniform. These models can easily be divided into strata (for each age group) but such models quickly become unwieldy once multiple strata are introduced. Standard childhood vaccination programs are typically well described by compartmental deterministic models.

Individual-based or *agent-based* models explicitly represent individuals potentially allowing for much greater differentiation in biology or behaviour. Such models are always stochastic and offer the most value when individual heterogeneity in transmission and the structure of interventions is important. For instance they allow individuals to be attached to groupings such as households or workplaces and can easily track features such as infection or vaccination history in great detail. Individual-based models tend to be considered for diseases such as pertussis, where they can more readily capture the effects of non-traditional vaccine programs, such as maternal or cocoon immunization, compared to compartmental models. However, model development time, the level of detail required in supporting data and the time required to run and adequately summarise simulations can all be much greater for individual-based models than comparable deterministic compartmental models.

Representing population heterogeneity

The simplest models assume that all members of a population are identical, and that they make contact with one another at random. Models developed to inform policy, however, generally need to represent additional population attributes such as age groupings, or vaccination status. The choice of population detail should depend on the specific research question and the data available to inform, or *calibrate*, the model.

Age-stratification of *compartmental* models can represent observed variation in susceptibility and infectiousness by age and allows for age-specific patterns of contact, such as increased mixing between school-aged children. This allows for a more accurate model of disease burden and risk, and allows exploration of targeted interventions, such as age-based vaccination schedules. Other features that might be considered include gender-differences (for instance in relation to sexually transmitted infections) or specific risk groups for transmission or disease. *Individual-based models* provide many more possibilities for representing heterogeneity, including networks of sexual contacts and spatial variation.

Depending on the time frame of the disease scenario, models may also incorporate *dynamic* aspects of population demography, such as births, deaths and aging. These processes are generally important in endemic diseases where the birth of susceptible newborns sustains infection through time. This allows models to capture the medium to long-term impacts of vaccination programs on population-level immunity, which is important for diseases such as pertussis where vaccination does not provide lifelong protection.

METHODS
Infection, immunity and interventions

Key points

- The major decisions in designing infectious disease models relate to categorising populations into distinct states relevant to the disease, determining allowed transitions between those states and including differences between subgroups or individuals that are influential in relation to transmission, disease outcomes or interventions.
- The susceptible-infected-recovered (SIR) model can be adapted to most infectious diseases with minor modifications to the basic structure.
- Vaccine interventions are often assumed to provide efficacy against infection leading to reductions in transmission. However, efficacy against disease and infection can differ and for some infections should be considered separately.
- Age-scheduling and duration of protection are important characteristics of vaccine-interventions, that need to be considered in model design in order to accurately compare alternative strategies.
- Models offer great advantages in terms of comparisons between multiple strategies. It is important, however, that these strategies are appropriately justified such as by outlining a pragmatic focus on feasible strategies or through a more aspirational focus on testing novel approaches to control.

Representing infectious diseases as models

Pathogens such as viruses and bacteria can infect humans through a variety of routes (e.g. airborne, faecal-oral, sexually transmitted, vertical transmission, vector borne) and differ markedly in the natural history of disease and infectiousness they induce. A model must capture these major biological features in order to accurately reproduce known epidemiologic behaviour. This is one of the main challenges with modelling but it can be helpful to think about it in terms of three distinct (but related) sets of decisions.

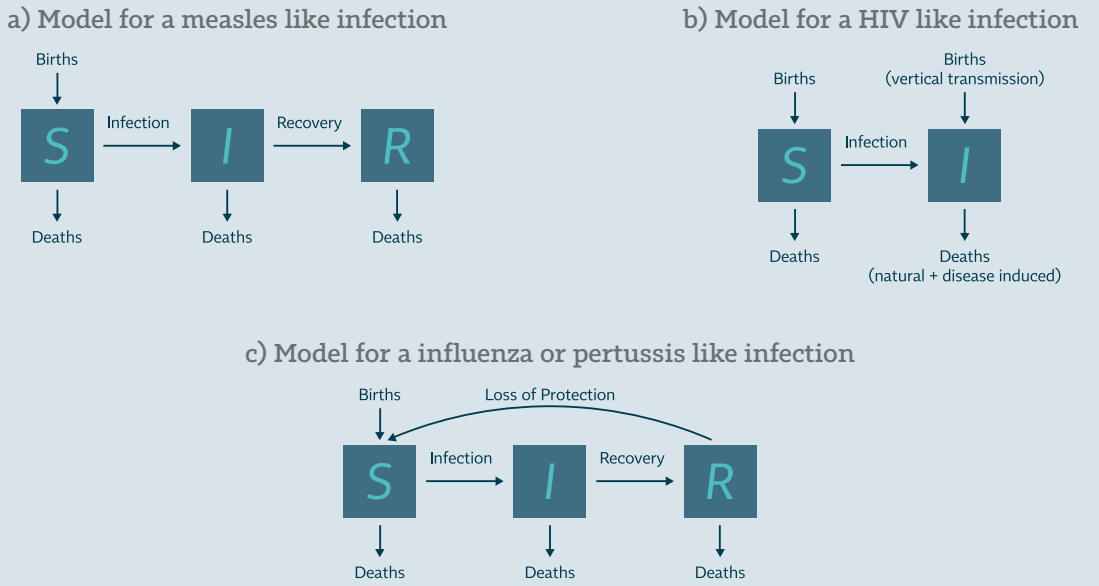


Figure 2: Basic model structures for infectious diseases with lifelong immunity, chronic infection and temporary immunity

1. Categorisation of the population into states

For an acute infection such as measles that induces life-long immunity (in the absence of vaccination), it is appropriate to consider that individuals are born susceptible, infected through exposure to others already infected in the population, and then recover with permanent immunity. This is the basis of the S-I-R model of disease (Figure 2a). In contrast, for a chronic infection such as HIV there is a possibility of being born infected (vertical transmission), and once infected, individuals remain so for the rest of their life. The appropriate model structure is an S-I model without recovery (Figure 2b). For infections such as influenza or pertussis that produce only short-lived immunity, multiple infections over the course of life are possible, and a structure such as S-I-R-S is appropriate (Figure 2c).

2. Determining possible transitions

In between the model states are arrows that determine movements of people between disease states. These arrows are closely related to the natural history of disease but are applied to the whole population so as to model disease dynamics. In the S-I-R model, there are two movements allowed – susceptible people may become infected, while infected people may become immune. In the S- I model, only the first of these is possible and on clearing infection individuals are immediately susceptible, while for an S-I-R-S model, movement back to susceptibility is allowed to represent loss of immunity with time.

Such a loss of protection may be primarily driven by antigenic drift, as in the case of influenza virus or loss of antibody with time, such as for pertussis following exposure to infection or vaccination. In addition to these primary transitions, we may allow additional movements, such as births and deaths to represent changes in populations in each state according to demographic change.

3. Accounting for heterogeneity

Once a basic model structure is chosen, one must decide on the level of detail required, particularly in relation to who acquires infection from whom (*WAIFW*). For instance, a model of respiratory infection spread can assume fairly uniform transmission within the population while for a sexually transmitted infection variance in, for example, partner change rates are key determinants of risk. When routes of spread other than human to human contact are implicated, additional elements are required in the model, for example representing environmental exposure to a waterborne disease, or the intensity and infectiousness of bites from a relevant vector population such as mosquitoes or flies.

Beyond these fundamental choices on model structure, other issues that may need to considered include accounting for multiple strains of a pathogen (e.g. for pneumococcus or dengue) or interactions between related diseases such as varicella and zoster. The choice of model structure should reflect these features where they are relevant to accounting for epidemiology and the effect of interventions on disease.

Representing vaccine interventions

Vaccine efficacy, or *direct protection*, is a measure of the proportionate reduction in disease attack rates among vaccinated participants in a randomised placebo-controlled trial (RCT), compared with the unvaccinated group, over a defined period of follow up. It is calculated as:

$$VE = 1 - \frac{attack\ rate\ (vaccinated)}{attack\ rate\ (unvaccinated)}$$

A 'perfect' vaccine would immediately transition immunized individuals to the recovered (*R*) state and offer life long protection from disease (as we assumed when calculating the *critical immunization threshold*) but this is almost never the case. In practice, vaccine protection is rarely superior to immunity following natural infection and, the mechanisms by which immunization reduces disease risk are varied. Vaccines may protect against *acquisition* of infection (*efficacy against susceptibility*), or modify the disease course in infected individuals resulting in asymptomatic or subclinical infection (*efficacy against pathogenicity*). While either mechanism may lead to the same observed outcome of disease prevention in a short-term clinical trial, these forms of protection have very different implications for disease control in populations over the longer term.

Capturing indirect vaccine protection

Vaccines that prevent acquisition of infection are likely to lead to a reduction in the prevalence of infection that increases with increasing immunization coverage. As the total number of infections falls, so does the number of new incident infections in the unimmunised population, a phenomenon known as *indirect protection*. Indirect protection tends to peak in the years immediately following vaccine introduction, a phenomenon known as the *honeymoon effect*, before reaching a more stable value. If the duration of protection is only short-term or the infection prevalence is very high (as with rotavirus), there may be little or no impact of indirect effects. A final point is that indirect protection tends to delay infection (i.e. increases the average age of infection) and can have negative consequences if severe disease is concentrated later in life, such as with maternal rubella infection.

Vaccines that don't perfectly protect against acquisition, may still modify the course of disease in ways that reduce infectiousness by decreasing (i) symptoms associated with transmission (e.g. sneezing, diarrhoea), (ii) peak viral or bacterial load, and/or (iii) duration of infectiousness. Such vaccines will also have *indirect protection* effects, extending the benefit of vaccine programs beyond the immunised group. This form of vaccine protection can be included in models as *efficacy against infectiousness*, with individuals with breakthrough infection posing a lower risk of infection to others than unimmunized infected individuals.

Models of vaccine action should be developed in response to all available evidence of the biological mechanisms of protection so as to accurately capture indirect effects. In addition to clinical trials, challenge studies in animal or human models, carriage studies, observational studies of disease course in immunised or unimmunised individuals, or population implementation studies demonstrating indirect vaccine effects should be considered.

Incorporating vaccine interventions in models

The mechanism(s) of vaccine action are incorporated in models as modifications to the rate of movement between compartments. Reduced susceptibility tends to be incorporated as reduced risk of moving between the S and I compartments (sometimes called "leaky" immunity) or by transferring immunised individuals directly to R ("all-or nothing" immunity). Over time, vaccine-derived immunity may be lost with movement back to the susceptible state incorporated. Reduced infectiousness is often captured by lowering the intrinsic infectiousness of immunised individuals (reducing β) or reducing the duration of infection (increasing γ). Efficacy against pathogenicity can be incorporated when clinical disease is specifically modelled as a reduced rate of movement into a separate 'disease' compartment.

Vaccination programs in particular need coverage and timing of immunization to be tracked. This is usually achieved through stratification of the model by immunization status and by age when coverage is age-targeted. In the simplest models, coverage is incorporated as a division of births by immunization status but more realistic models for policy typically include age structure, so that immunisation can be applied consistent with local scheduling and timeliness. Various alternative schedules, including variations on age-scheduling, booster doses and catch-up campaigns can then be readily tested within such frameworks for comparison of their impacts on disease burden and their value for money.

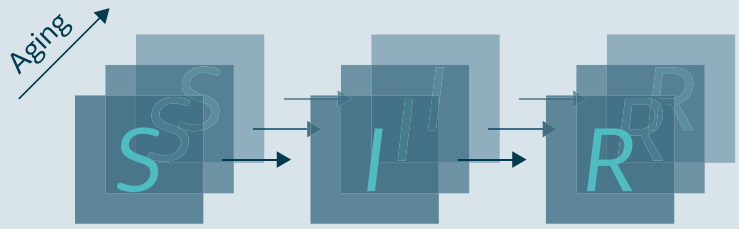
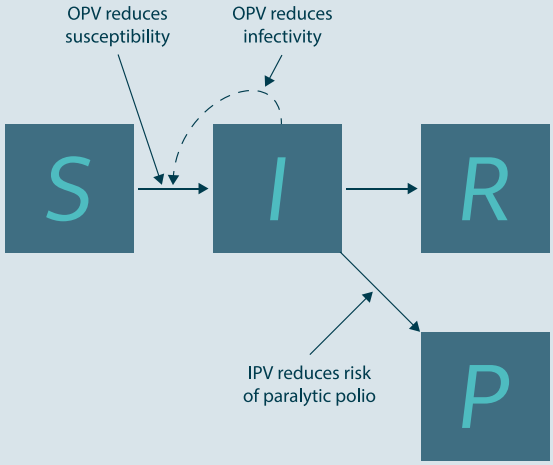


Figure 3: *Schematic indicating how age-structure can be introduced through model stratification*

Case-study: Polio Immunisation

Polio clearly demonstrates the importance of vaccine mechanisms for population level vaccine program effects. The Salk inactivated polio vaccine (IPV) protects immunised individuals against development of paralytic polio, should they become infected with the virus, while still allowing ongoing infection and transmission. For this reason, IPV can only provide effective protection against disease in populations where vaccine coverage will be reliably sustained at high levels. In contrast, the Sabin oral polio vaccine (OPV) provides some measure of protection against acquisition, but more importantly controls virus replication and shedding from the gut, which is the site of infection. As such, it is able to limit transmission of any wild type virus strains that continue to circulate in a partially vaccinated population. The unfortunate down side of OPV is the risk of reversion of attenuated vaccine strains to neurovirulent forms, resulting in observed cases of vaccine associated paralytic polio and continued circulation of vaccine-derived virus in the environment.



Box 1: *Differential impacts of vaccines on transmission and disease in respect to Polio. Additional complexity relating to OPV-strain transmission is not shown.*

Using models for scenario analysis

A key use of models is to explore alternative intervention scenarios, such as vaccination, quarantine or school closures. Comparisons of many scenarios are readily possible, allowing models to be used to rank the likely impact of a range of different interventions on a pre-specified outcome such as disease incidence. For instance, a model might be used to compare impacts of 1 or 2 doses of varicella vaccine given at different age-schedule points with the aim of determining which option is projected to be the best in reducing morbidity from VZV infection. Feasibility is an important consideration when scenarios are used to inform policy decisions, and implementation decisions used for the simulation, such as vaccination coverage or timing, should be clearly outlined.

Although pragmatic, feasible alternative scenarios are often selected for simulation, it is not unusual for aspirational 'best-case scenarios' to be considered. Whether achievable or aspirational, the reasons for exploring particular scenarios should be outlined and justified with a clear summary of the scenarios simulated provided in the methods section.

Scenarios can also be used to explore which assumptions best explain existing disease epidemiology or in an effort to reflect known uncertainty around model inputs. This process will typically involve a quantitative comparison between model simulations and one or more sets of data (for instance age-specific seropositivity to pertussis at 3 distinct time points). Within the methods section of a modelling paper, you expect to see the characteristics of these scenarios clearly described including such information as the population conditions, infection characteristics and control measures applied. Additionally, the way in which the simulations are compared with data should be clearly explained as this often differs between studies.

METHODS
Model assumptions, structure and uncertainty

Key points

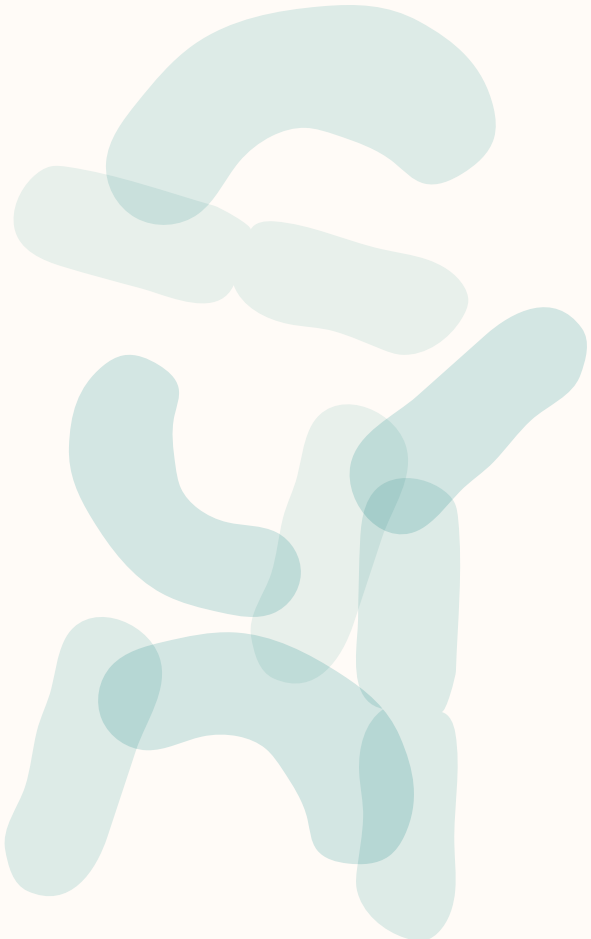
- Models typically make use of a number of assumptions about how transmission interventions work. Ideally, each assumption is justified in terms of good quality evidence but at the very least, points of difference from existing work should be mentioned and the evidence underlying these decisions presented.
- Most inputs to models are imprecise making it important to reflect related uncertainty in key outcomes. This is typically done through one-way or probabilistic sensitivity analysis and may be supplemented by scenarios comparing impacts of alternative model assumptions.
- A further level of robustness can be added by applying one model to datasets from multiple settings or multiple models to data from a single setting. This approach has some similarities to meta-analysis but is time-consuming and rarely applied in practice.

Deciding on key model assumptions

Designing a model involves deciding which elements are most crucial for capturing the disease epidemiology and the effect of interventions in relation to the research question. There are two key processes here – firstly, details that appear unimportant for the research question are excluded altogether (e.g., gender is often not considered in models of respiratory transmitted infections). Secondly, each included detail must have a precise quantitative definition within the model, even though existing knowledge may only partially inform these choices.

Ideally, each such decision and related assumptions should be identified and justified with reference to evidence. Wherever possible, this evidence should be directly relevant to the population and disease under study and based on a valid study design or synthesis of such evidence. In addition, the way information is presented in such literature may not match the model structure and timescale and require transformation: for instance study data might provide the proportion of individuals who became seronegative to a given antigen over a decade, whereas a model might need to implement this as an annual rate. Where good quality evidence is not available, expert opinion or simple and general comparisons (cf. *Occam's razor*) can still be useful, particularly in regard to identifying potential policy options with poor outcomes. For instance, impacts of border screening on pandemic influenza were quickly identified as being relatively ineffective despite very little empirical evidence being available.

As models often build on previous modelling studies, it is typical for significant detail to be provided only for assumptions that are seen as contentious or different from previous work.



Dealing with uncertainty in model assumptions

Often, there is considerable uncertainty regarding certain modelling decisions, either due to a lack of data or multiple imprecise data sources that may give conflicting answers. If an objective approach to consideration of uncertainty is not taken, there is potential for bias in favour of "desirable" outcomes, analogous to publication bias in other areas of medical science. As part of the sensitivity analysis section of modelling papers, there should be consideration of such uncertainty through one or more of the following techniques:

- Many simulations for a single set of values (*stochastic* models); this is particularly useful when individual variation is important, such as in spread of a newly emerged infection to other countries.
- Comparison of model outcomes when a given input assumption is varied over a range (defined, where possible, by data or expert opinion); for instance a case-control study may have been used to estimate vaccine effectiveness in the range 40%-70%. This uncertainty should be explored by reporting model outcomes across this entire range, rather than focusing only on for example the mid-point.
- *Probabilistic sensitivity analysis*, where many input values are simultaneously sampled from probability distributions, producing a "cloud" of results consistent with input uncertainties; for instance this is used in economic evaluations to show the proportion of simulations that could be considered cost effective for varying cost-effectiveness thresholds.
- *Comparisons of extremes*: where contentious parameters are alternately set to values that are favourable and unfavourable to an intervention, to assess the robustness of outcomes, particularly those with clear policy relevance such as economic evaluations. For instance, one might compare a situation where all vaccine related parameters (efficacy, coverage, duration of protection) are set to minimums against where they are set to maximums to see how this influences overall impacts on disease burden or value for money.

Inclusion of such examples of uncertainty or sensitivity analysis indicate that the uncertainties have been considered in a meaningful and robust manner. In some cases, the actual model structure may be in some doubt (for instance to what extent is naturally derived immunity important in describing the epidemiology of human papillomavirus infection?). In such circumstances, comparisons of alternative model structures can be conducted. Such comparisons can help to exclude structures that do not describe existing data well and suggest which structures are most appropriate. In circumstance where several model structures describe the data well, such findings can provide an impetus to further empirical research to inform the correct choice. Another application of this idea is to take several differing models and use them to investigate the same question as another way of assessing robustness (this approach has been widely applied in the HIV field and to a lesser extent with subjects such as rotavirus vaccination).

METHODS
Comparisons with data (inputs, outputs)

Key points

- Data sources and their relation to model inputs (and sometimes outputs) should be clearly outlined within papers, ideally through a parameter table that provides descriptions, values and references of sources for the data.
- Calibration and validation are approaches for constraining model outputs to observed data and testing the predictive validity of the model respectively.
- Some form of calibration and validation is required in assessment of predictive models.

Description of data sources for characterization of the population, epidemiology and interventions

Models of vaccine preventable diseases make use of a variety of data sources, primarily to inform model inputs, but also for use in directly *calibrating* or *validating* models (described in more detail below). Typically data sources are a mix of estimates provided by the literature (for instance vaccine efficacy as estimated in clinical trials), population information such as birth and death rates sourced from national statistics offices and then more disease specific information such as notification, morbidity and mortality data. Data sources such as serosurveys or pathogen-carriage surveys (e.g. meningococcal disease) are often important for establishing dynamics of infection, particularly where reportable disease cases represent a small and biased subset of infection exposures. For instance, most hospitalized cases of pertussis will be in young infants but infection is much more widely distributed across the age spectrum, as can be seen from serosurveys.

In terms of presentation, each data source should be clearly described, and its use in the model explained. This information is often briefly summarised in a parameter table, where *parameter* names, values (+ranges) and sources are listed. Ideally this table should be supplemented by a discussion of key assumptions and justification of choices of source data in the text. Absences of clear descriptions of sources and parameter values either in the main text or supporting information should be cause for concern in terms of validity of assumptions. A more subtle concern is in regard to source referencing, where not infrequently the references will point to earlier modelling papers, rather than primary data. This practice may be justified (e.g. building on previous work by the same group) but can be a sign that epidemiological assumptions have not been carefully reviewed.

Table 2: Example of parameter table in relation to waning of immunity after measles immunization (adapted from Wood, JG et. al. Vaccine. 2015. 33(9):1176-81 doi: 10.1016/j.vaccine.2014.12.071)

Parameter	Symbol	Value (Range)	Source
Waning rate (after one dose)	ω_1	1/50-1/20 per year	[7,20]
Waning rate (after two doses)	ω_2	1/200-1/80 per year	[7,10,20]
Waning rate (immunity from infection)	ω_n	0	Absence of good evidence to contrary
Proportion seroconverting (1st and 2nd dose)	q_1, q_2	$q_1 = q_2 = 0.97$	Consistency with serosurvey values for 1-4 year olds and similar to estimates from recent MMR/MMRV trials [21]

Comparing models with data: Validation and Calibration

Some kind of comparison with data is essential in any policy relevant modelling study, although this is harder with emerging infections due to the lack of prior observations. Typically these comparisons are divided into two stages with different purposes. Model calibration is a process by which model outcomes are compared with data, with the aim of refining model inputs and/or structural assumptions so as to describe the data as well as possible (without over-fitting). For instance, one might aim to have the model as closely as possible reproduce the incidence of zoster disease in Australia, by altering the age-specific rates of zoster reactivation within the model. This process is essentially similar to statistical procedures such as regression whereby a line of best fit is produced – in this case it's just that the underlying model is a bit more complicated. Alternatively a more qualitative approach that aims to match to certain major features of disease epidemiology, such as epidemic cycle lengths in the case of pertussis might be used as a constraint to guide appropriate sets of model inputs.

Validation on the other hand aims to test the ability of models to predict disease outcomes not used in the calibration process. For instance, a model of varicella infection in Australia might be calibrated to data prior to the introduction of the vaccine and then simulated forward in time to see whether it reproduces post-vaccination changes in disease burden. Validation may also be qualitative or use more formal quantitative approaches (e.g. *cross-validation*) but given models are often intended for use in a predictive manner, some form of validation of model predictions should usually be performed.

RESULTS
Presentation of results and uncertainty (parametric, methodological etc.)

Key points

- The results section should present in graphs and tables both the main outcomes of the paper and intermediate results such as the model validation and calibration.
- When many scenarios are being compared a summary of results across all strategies should ideally be shown before focusing on a subset for more detailed presentation.
- Uncertainty around results to be presented through, for instance, Tornado plots for one-way analysis and approaches such as 95% uncertainty ranges for multivariate analysis.
- Where assumptions are quite controversial, findings should be compared with those using alternatives assumptions in a scenario analysis.

Main outcomes and scenarios

The presentation of results will vary depending on the main purpose of the paper. For instance if the study aims to describe existing disease epidemiology, the results section should focus on presenting fits of different model scenarios to the data and assessment of the quality of these fits. If, for example, determining the duration of vaccine-derived immunity to pertussis is the main focus, one might expect to see tabulated estimates of this parameter for comparison models that make differing assumptions about how mild infections contribute to transmission. If the focus is on assessing a new vaccine intervention, then scenarios will be used to explore how variations on implementation of this intervention compare in terms of for example, incidence of disease requiring hospitalisation.

Either within the results section directly or supporting information, graphs of how key outputs (typically disease incidence and/or morbidity or mortality) are projected forward in time should be shown for at least a key set of strategies. Often these results are presented over a timeframe of many decades and it is important to remember that the validity of these predictions will decrease over time due to changes in population structure, behaviour and maintenance of immunity. In some cases study authors will focus on results at a post-vaccine "equilibrium", without alerting readers to the fact that this does not occur until several decades into the future. Both authors and readers should focus on more immediate model predictions (within the next decade) as these are likely to be more robust, while considering potential longer term effects including unintended adverse consequences of interventions.

We comment more extensively on economic evaluations at the end of this document but note that as these are often most closely relevant to policy, there is an additional need for presenting relative contributions to health benefits gained and costs saved, as well as impacts of uncertainty in these analyses. Often there can be a tendency to single out a "base-case" intervention. This can be quite reasonable - for instance there is one intervention strategy that is more feasible and more likely to be acceptable to policy makers than the rest. Often, however, it is better for results from all strategies to be presented briefly. This process provides the rationale for selection of favoured strategies for more detailed presentation, having demonstrated which are the most efficient or effective in relation to key outcomes.

Sensitivity analysis

The effects of uncertainty analysis can be presented in a number of ways. Generally this involves choosing a set of input values, generating outputs of interest (such as disease incidence, mortality or costs) then repeating the process several (or many) times with different sets of input values. Sensitivity analysis aims to determine which of the uncertain inputs have the greatest influence on model outputs, and our subsequent conclusions. In *one-way* sensitivity analysis, a single input is varied at a time, with output sensitivities then summarized through *tornado plots* or more complex measures such as *partial correlation coefficients*. Tornado plots represent both the direction (increase or decrease) and relative magnitude of changes in outcomes that result from one-way sensitivity analysis on a series of inputs, providing a comparative overview of which inputs are most influential (see Figure 4 below for an example).

Multivariate approaches, however, are preferred for characterizing combined uncertainty around a given outcome. A full understanding of input-related uncertainty involves establishing probability distributions for each parameter and then using a *Monte-Carlo* sampling approach to simultaneously draw input values from each distribution. Outcomes are then generated by running the model, typically 1000s of times, to generate a cloud of results representing the

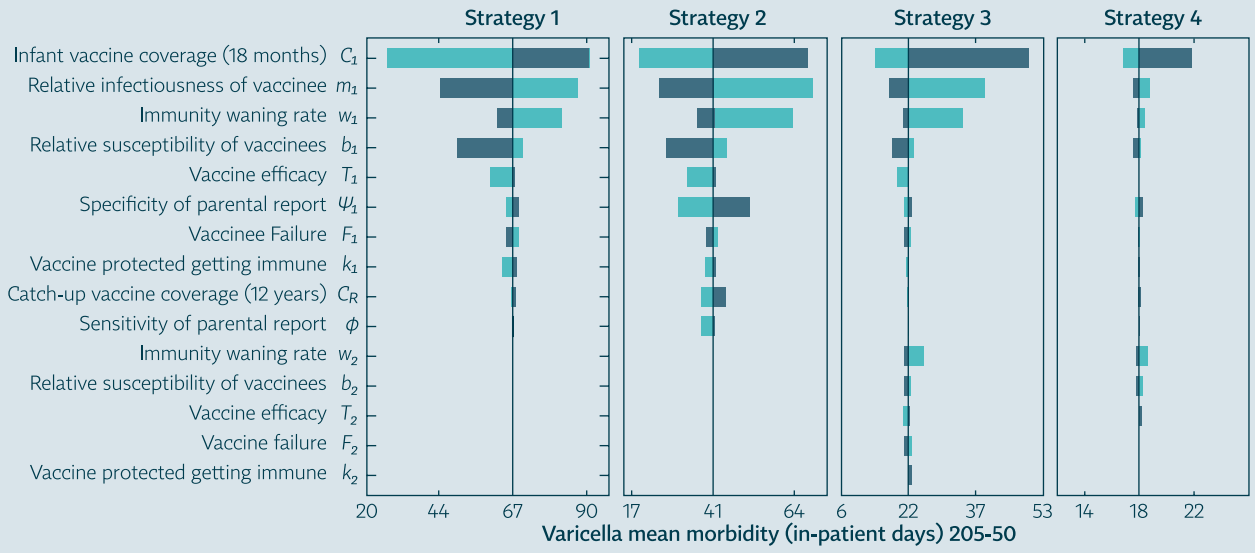


Figure 4: *Example of tornado plots combined with scenario analysis used to assess sensitivity of predictions of varicella morbidity under various vaccination options (source: Gao, Z et. al. Epidemiol Infect. 2015 143(7):1467-76. doi: 10.1017/S0950268814002222)*

resulting uncertainty in model outputs. Referred to as *probabilistic sensitivity analysis*, this approach is commonly used in sensitivity analysis for cost-effectiveness modelling. In some cases, it may be combined with comparisons with data through a calibration process in order to refine predictions of uncertainty. An example of such refined uncertainty is presented in Figure 5a below, where probabilistic sensitivity analysis was first conducted using millions of simulations, before these were constrained to reproduce key features of pertussis epidemiology in Australia. Only those sets of inputs that achieved this were retained, leading to a refined set for use in further analyses.

Scenario analyses also form an important way to assess uncertainty in model outcomes. For instance the impacts of pneumococcal conjugate vaccines on all-cause otitis media were unclear from vaccine trial results but influential in terms of cost-effectiveness estimates. In Figure 5b below, impacts on health and cost savings for the 10 and 13-valent vaccines are shown over a wide range of possible effects on these outcomes, while representing combined uncertainty for other variables. This kind of approach can also be used to test sensitivity of the model to design decisions, such as the number of different disease states included and allowed movements between them. For instance one might compare the impact of a vaccine program with lifelong durations of immunity (S-I-R type model) as opposed to an immune duration of 10 years (S-I-R-S type model).

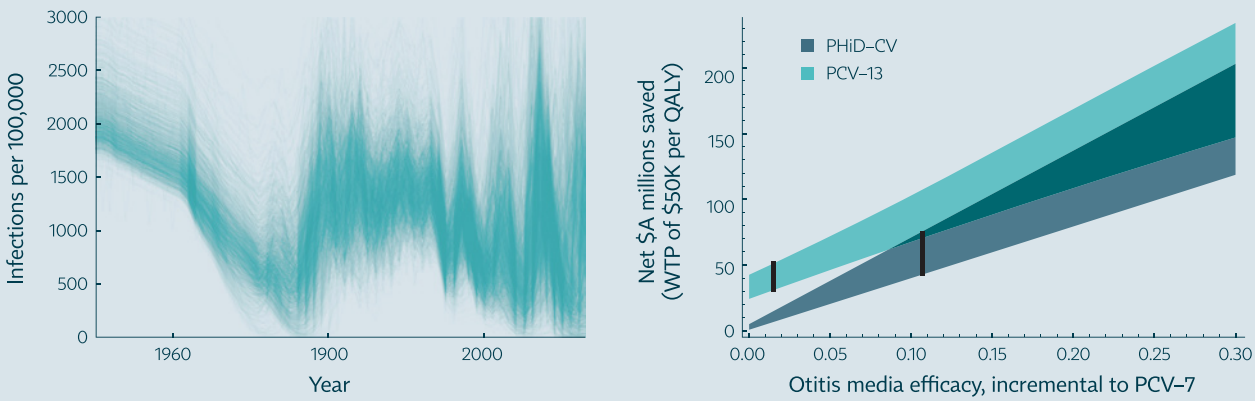


Figure 5: *Examples of probabilistic sensitivity analysis: (a) modelled incidence of pertussis infection in Australia, where plausible variation in inputs was used to generate millions of simulations, from which a subset consistent with observed features of pertussis epidemiology in Australia were retained; (b) comparison of 10-valent and 13-valent pneumococcal vaccines as a function of their efficacy against otitis media, incorporating multivariate uncertainty relating to other inputs [sources: (a) Campbell, P et. al. Vaccine 2015 (in press) doi: 10.1016/j.vaccine.2015.09.025, (b) Newall, AT et. al. Vaccine 2011. 29:8077–85 doi:10.1016/j.vaccine.2011.08.050].*

DISCUSSION
Contextualisation (other models, current knowledge, limitations)

Key points

- Model results need to be discussed in the context of existing modelling and empirical research on the topic.
- Models are simplifications of reality and should not be expected to match all relevant data sources. However, in relation to the primary outcomes from the model, it is important to evaluate how these compare with other data sources and studies.
- Uncertainty around key outcomes should be highlighted in the discussion. If a study focuses entirely on point estimates of outcomes instead of ranges you should be sceptical.
- A frank and detailed discussion of limitations of the model is important. Ideally this should go beyond just noting limitations to discuss how results would be expected to change if other assumptions or additional details had been included.

Model results in context

Like all scientific studies, the discussion needs to place modelling results in context. Typically there is a body of existing modelling work and then various empirical studies such as trials, observational studies and routinely collected data that need to be discussed. This can be somewhat complex as a model will generate many results and some of them will not match closely with empirical data. These issues are typically covered in the limitations section but it is important to remember that it is not generally the goal of models to capture all details of disease epidemiology accurately. For instance a model of a new immunization program may not be designed to capture seasonal fluctuations in incidence but still accurately assess the average impact on disease incidence. Such a model would be perfectly fine for use to estimate the overall change in the burden of disease and direct costs associated with disease morbidity. However, it would not be able to accurately assess impacts on hospital surge capacity and if this were an important consideration, would need revision to include seasonal components.

For studies that aim to inform policy, additional discussion of the level of realism and uncertainty in findings is very important. Input values, the choice of model states and possible transitions and the limitations of existing data all contribute to uncertainty in the main outcomes from models. From a policy perspective it is important that the implications of variation around the main findings are discussed. It could be for instance that the base-case analysis and the majority of simulations support introduction of a new vaccine program but that a sizeable majority of model outputs (say 30%) suggest that the proposed program would not be cost-effective. It is particularly important that this kind of finding is explicitly mentioned in both results and discussion sections to avoid potential bias towards positive base-case findings.

In contrast, if a study focuses discussion on very specific quantitative results in relation to its policy-related findings, then you should have concerns about whether uncertainty has been adequately addressed. For instance you might find a paper suggesting that following an intervention for pertussis, incidence peaks at 90 per 100,000 population in 2016 and then declines to below 30 per 100,000 population after 2025. This sort of detail appears important but is essentially arbitrary – even the simplest of uncertainty analyses is likely to produce numbers that are substantially different to these estimates. While uncertainty doesn't necessarily have to be addressed in terms of a balance of probabilities, it is important that it features just as prominently as quantitative statements of outcomes in the discussion section. The influence of programmatic factors like variation in coverage must also be clearly discussed since they can be influential in policy decision-making. Models can also be used to provide guidance on the specific conditions under which a given intervention would be useful, or the circumstances under which negative consequences might occur, which may have implications for evidence gathering or program design.

Limitations

Models are simplifications of real world systems, based on assumptions believed to be reasonable. Even complex individual-based models only include a fraction of potential factors relevant to transmission and it is therefore important to clarify and justify omissions from models. Explicit omissions are typically well described (for example, omission of a latent disease state), more implicit assumptions may be influential but not detailed. For instance in modelling the impact of varicella vaccination in the USA, links between varicella and zoster epidemiology were not explicitly considered and dismissed in limitations as outside the scope of the study. Later studies, by contrast, suggested the interaction was of critical importance to cost-effectiveness assessments. It's important to ask when reading the limitations section whether plausible results are excluded due to the structure or assumptions used in a model.

An example of a reasonably detailed limitations section is given in Box 2 below

> Our predictions are sensitive to several key assumptions regarding varicella epidemiology and vaccination programmes. We assumed that receipt of the second dose was independent of the first which may lead to over-estimates of coverage with 51 dose of vaccine and hence impacts of two-dose programmes. Other important assumptions include setting the severity of breakthrough cases to be lower than wild-type infections (contributing one tenth as much in morbidity calculations), based loosely on post-implementation data collected in the USA [27]. Other modelling analyses have also assumed low morbidity due to breakthrough infections [15] but data to establish the severity of breakthrough disease and whether the subsequent risk of zoster is identical to that following wild-type infection remain limited and will need to be revisited as vaccine programmes mature. Most modelling studies, including ours, assume lifelong immunity against varicella re-infection following natural infection [9, 12, 15] but the validity of this in the absence of frequent exposure remains to be evaluated. The absence of lifelong immunity would influence estimates of the reproductive number and also the projected impacts of vaccination.
>
> Our simulations apply the Hope-Simpson hypothesis [31] regarding protection against zoster from varicella exposure, which is supported by data from several other observational studies [32–34]. The Shingles Prevention Study [18] offers definitive evidence that boosting with a high-dose vaccine reduces the risk of zoster, but the effect of reduced exposure to varicella on zoster incidence at the population level is still uncertain, with both the incidence and duration of boosting unclear. A recent review of observational studies of boosting [35] suggests that immunological correlates of boosting show little evidence of an effect beyond 2 years post-exposure, indicating that endogenous boosting may be more important in sustained zoster protection than assumed in models. Validation of zoster trends also remains difficult due to limitations in the design and duration of current surveillance programmes. A recent retrospective study of Medicare claims conducted by Hales et al. [14] suggests a continuous rise in age-standardized zoster incidence in the over-65 s in the USA from the early 1990s, predating VZV immunization. Despite these uncertainties, we note that the zoster predictions in this study were insensitive to coverage and strategy changes. Minor limitations include the reliance on estimates from studies in other settings [23–25] regarding parental recall of their child's varicella infection and vaccination history and limited data [9, 36] underpinning estimates of vaccine efficacy parameters, particularly for the second dose.
>
> ***Box 2:*** *source: Gao, Z et. al. Epidemiol Infect. 2015 143(7):1467-76. doi: 10.1017/S0950268814002222*

As with most areas of public health, both epidemiology and the effect of interventions can vary strongly between settings. For this reason, care must be taken when the findings of a model configured around the circumstances relevant to one context are extrapolated to an unrelated setting. For instance, potential impacts of rotavirus vaccines in Australia should not be suggested as directly relevant to such a program in Indonesia, due to differences in the age-distribution of cases and morbidity and the potential for lower vaccine efficacy. More subtle issues, such as the pattern of bacterial carriage with age might lead to quite different population effects from conjugate pneumococcal vaccine in otherwise similar settings. More confidence in extrapolation can be gained if data from several settings have been compared to identify commonalities, and if extensive uncertainty and sensitivity analyses have been conducted.

Checklist box

Concept	Recommendation	Is this present and to what degree?
Purpose	The rationale for using the model should be clearly described including discussion of complexity and relationship to prior models.	
Relevance	The scope and relevance of the modelling study to policy should be clearly described.	
Paradigm	The modelling paradigm (deterministic, stochastic, individual-based etc.) should be clearly identified and supported through schematics, equations and model code where possible.	
Stratification	Key risk factors used to stratify model states (such as demographic or biological risk factors) or to distinguish risk in individuals should be clearly identified.	
Vaccination	Assumptions regarding vaccine interventions should be clearly articulated including parameters affecting coverage, efficacy and duration but also how the vaccine is assumed to protect individuals (prevents infection or just disease?).	

Concept	Recommendation	Is this present and to what degree?
Assumptions	The nature of key assumptions and the evidence underpinning them should be described along with additional relevant details such as parameter tables and associated statistical analyses.	
Uncertainty	Uncertainty in inputs and assumptions should be explored and presented through some combination of sensitivity and scenario analysis. Presentation could take the form of figures or simply ranges defining uncertainty around key outcomes.	
Comparison	Some comparison with data should be undertaken both to refine uncertainty and as validation of model predictions. The latter is particularly important if the model is meant to be used for prediction (rather than estimation).	
Discussion	Model findings should be compared with relevant literature, data and evidence and differences given due consideration.	
Limitations	A detailed discussion of limitations associated with model design and inputs should be presented with guidance as to the likely effects of omissions.	

Health economic aspects

Key points

- Health economic evaluations in developed settings focus primarily on the incremental cost-effectiveness of new interventions in comparison to current practice.
- In relation to vaccines, herd immunity and dynamic changes in epidemiology can substantially change the outcomes from economic evaluations.
- Additional assumptions to look at carefully include the components of disease burden included in the analysis and assumptions around QALY benefits from mild but common disease.

Basics of economic evaluation in healthcare

Economic evaluations in healthcare seek to value changes in health gains and healthcare (and related) costs associated with changes in practice, such as the introduction of a new vaccine program. These evaluations seek to assess whether health gains associated with a new intervention provide value for money compared with current practice or other reasonable alternatives. Most economic evaluations in high-income countries focus on estimating the incremental cost per quality adjusted life year (QALY) gained and are expressed through the incremental cost-effectiveness ratio (ICER). This measure implies a comparison between a proposed intervention and current practice (or no intervention) calculated as the

$$ICER = \frac{Cost_{int} - Cost_{curr}}{QALY_{int} - QALY_{curr}}$$

and presented as for instance $/QALY gained. As part of these calculations, costs and benefits that occur in the future are typically discounted back to their present day "value": at present the PBAC advises discounting at 5% per year for both costs and benefits. In other countries the rates can differ and may be subject to change as has happened in recent years in the Netherlands and the UK. Choices around the discounting rate can have a large impact on the cost-effectiveness of vaccination programs due to different timing of costs and benefits. Typically proposed new interventions are more costly and more effective than current practice (although this is not necessarily the case) and in most countries there is some notional range of an acceptable threshold ICER value, although an explicit threshold is not given in Australia.

Key considerations for infectious diseases and vaccine programs

Infectious diseases raise some issues in relation to cost-effectiveness that are not necessarily present for other diseases. Here we highlight several issues of importance in evaluations of vaccine programs, which should be considered carefully when reading published studies:

1. Dynamic impacts on disease epidemiology

Herd immunity effects are a key reason for using infectious disease models to underpin economic evaluations of vaccine programs. However, it's important to recognise that the herd impact is often complex and may vary with key model assumptions. Parameters such as the efficacy of the vaccine against infection and the duration of immunity both strongly influence the size and duration of herd immunity effects but are often not measured in clinical trials. Even if a dynamic model is not used in the cost-effectiveness analysis (e.g. most analysis of conjugate pneumococcal vaccine effectiveness), analyses should account for predictable consequences of a vaccine intervention, such as resultant changes in the characteristics of disease causing strains

2. Determining disease burden for pathogens with non-specific disease syndromes

A number of significant infectious diseases cause a wide spectrum of clinical presentations, ranging from mild illness to death. In addition, the associated symptoms may be shared with a variety of other infectious and non-infectious causes. Conventional surveillance tends to underestimate the disease burden from such infections (e.g. influenza and rotavirus) with disease burden estimates relying on additional statistical analysis to infer "attributable disease". For instance, influenza is not often accurately attributed as a cause of death, forcing reliance on the syndromic description of 'influenza and pneumonia' mortality for more realistic estimates of disease burden. Associated uncertainty in outcomes such as disease burden estimates and incremental cost-effectiveness, needs to be carefully represented when considering new vaccine programs when estimating the disease burden attributable to an infectious disease.

A second area of concern is in relation to the assumed proportion of a disease syndrome that is attributable to a given pathogen. For instance, the assumed proportion of community acquired pneumonia that is assumed attributable to strains included in 13-valent conjugate pneumococcal vaccine can have a tremendous impacts on the QALY gains predicted from introducing an elderly program with this vaccine.

3. Large QALY benefits derived from prevention of mild disease

New vaccines are often targeting infections that are common but where most disease is mild and may not involve significant health-care utilization. The impact in a cost-effectiveness calculation will then come through QALYs changes, that are estimated by the product of the duration of illness with the quality of life (QoL) score while ill and the number of such events prevented. A small QALY gain of 0.01 applied to one million mild cases will produce a similar QALY estimate to prevention of 500 child deaths. Aside from whether this reflects society's preferences, the impacts on mild disease often have a poor evidence base in terms of both the magnitude of the QALY score and the frequency of events (given these are typically not medically-attended).

Presentation of methods and results

In addition to the comments in previous sections, economic evaluations should clearly tabulate model inputs, with base values and relevant ranges (and/or distributions) and sources. As economic evaluations are very important inputs to the policy arena, transparency is very important as is extensive assessment of uncertainty around key findings. At a minimum, this should include probabilistic sensitivity analysis but ideally should be accompanied by the use of scenarios to present the impact of critical assumptions around vaccine impact (such as duration of immunity). Additional tests of the robustness conclusions are also advisable, which might for example take the form of presenting worse and best case scenarios for the effect of an intervention and level terms with the main results.

Glossary

Acquisition: Infection of a host.

Basic reproduction number (R_0): The average number of secondary infections caused by a typical primary case in a fully susceptible population (i.e. with no prior experience of that infection).

Calibrate: Adjust model inputs so as to closely match model output to one or more sources of data.

Compartmental or state-based: A type of model commonly used in analysis of vaccine-preventable diseases, where the population of interest is separated into one of number of "disease states" considered relevant to infection with that pathogen.

Cost-effectiveness evaluations: Evaluations of the value for money provided by changes to health practice such as immunization programs.

Critical immunization threshold: An approximate value for the proportion of individuals that needs to be effectively immunized to achieve elimination of infection.

Deterministic: A process (such as infectious disease model) whereby for a given set of input values, exactly the same set of output values will always be returned.

Direct protection: The reduction in disease risk observed in immunised individuals compared with unimmunised individuals resulting from antibody or cellular immunity induced by vaccination.

Duration of immunity: The period of time for which an individual is protected against infection as a result of prior immunization or infection.

Dynamic: A process that changes in time but more specifically in the context of infectious disease models, where the population risk of infection can change as a result of interventions. Such models can capture herd immunity effects in contrast to "static" models that only consider individual-level benefits from interventions.

Efficacy against infectiousness: The efficacy of a vaccine against onward transmission resulting from reduced symptoms, peak pathogen load or duration of infectiousness, given breakthrough infection.

Efficacy against pathogenicity: The efficacy of a vaccine against symptomatic disease in an individual when infection occurs.

Efficacy against susceptibility: The efficacy of a vaccine against acquisition of infection occurring given exposure (analogous to sterilizing immunity).

Endemic: A disease that is continuously present in a population, often with relatively stable prevalence.

Epidemic: A disease showing exponential growth over typically a limited duration, before declining.

Herd immunity: The level of collective immunity in a population, which can be influenced through interventions such as vaccination resulting in changes in infection prevalence and the potential for disease elimination.

Honeymoon effect: A description of the initial period of (large) reductions in disease incidence following vaccination, which may not be sustained in the longer term if vaccine coverage is below the critical immunity threshold.

Impact: Changes in infection or disease patterns through for example a vaccination program. This is typically measured through changes in incidence of infection or measures of more severe disease such as hospitalization and death.

Indirect protection: The extra protection afforded to individuals through herd immunity, reducing infection risk. A vaccine program that provides indirect protection will result in a lower prevalence of infection and disease in the unimmunised proportion of the population than was observed before vaccine introduction.

Individual-based or agent-based: an approach to models, in which individuals are explicitly characterized, with the potential for greater detail in describing infection risks and the impact of interventions.

Monte-Carlo sampling: The process of repeatedly drawing values from a probability distribution for use in calculations. This approach is used in infectious disease modelling either in assessments of uncertainty or sensitivity, or in stochastic models as a means of determining the movement of the population between disease states.

Naïve: An individual who has not previously been exposed to an infection (or a vaccine against this infection) and as a result has no immunity against it.

Occam's razor: The principle that explanation (or models) should not include more assumption than needed.

Ordinary differential equations: A branch of calculus that describes equations where a function is related to its derivatives. More specifically, this means that they are useful to describing physical and biological systems where the rate of change depends on the current state of the system. In relation to infectious disease models for instance, movement out of the susceptible compartment depends on the current prevalence of both infectious and susceptible individuals.

Parameter: A value that is used as input to a model, which typically has some empirical basis. For instance a key model parameter for measles transmission is the average duration of infectiousness.

Probability distributions: Functions or tables that define the probability of a given quantity taking one of an allowed range of values. Commonly applied distributions in relation to modelling parameters include Poisson distributions (count data such as the reproduction number), Gamma distributions (duration of infection) and log-normal distributions (relative risk of infection given vaccination) as indicated in Figure 6 below.

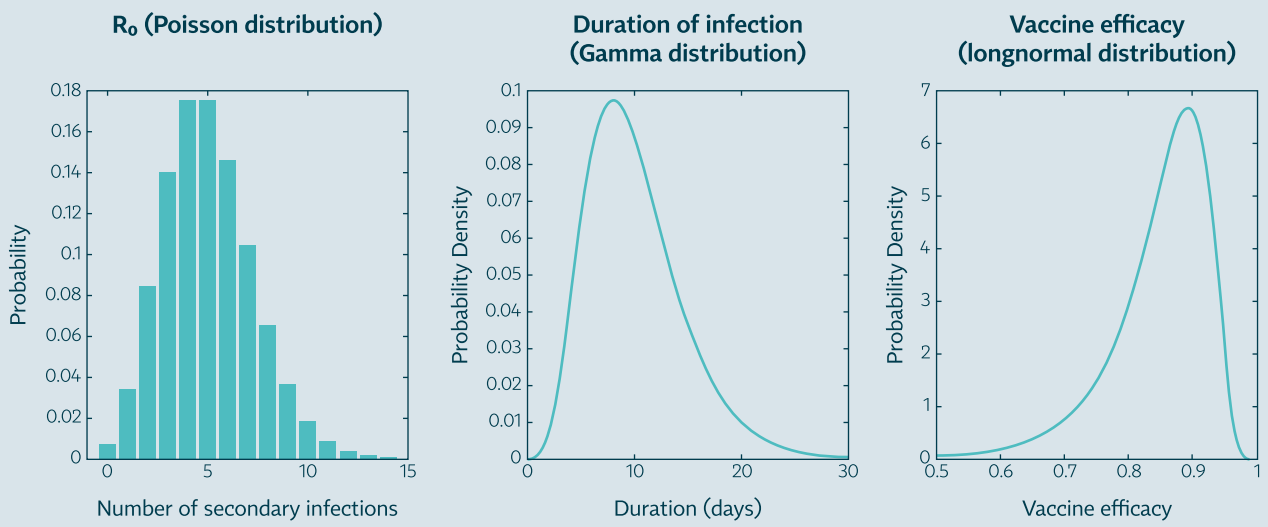


Figure 6: *Examples of probability distributions used for key parameters in models of vaccine preventable diseases.*

Reproduction number: The average number of secondary infections caused by a typical primary case in the population of interest, otherwise known as the 'effective' reproduction number. Unlike the 'basic' reproduction number, this value is influenced by the level of immunity in the population.

Resistant: A state of sterilising immunity, in which an individual is perfectly protected against acquisition of infection

State: A subgroup of the population associated with an important component of infection or disease.

Stochastic: A process (such as an infectious disease model) where outcomes vary according to pre-defined probability distributions.

Stratified: Refers to the division of the modelled population into subgroups. Stratification often relates to common epidemiological variables such as age and gender.

Transmission: The transfer of infection from one host to another.

WAIFW: Who acquires infection from whom. This refers to the notion of incorporating different rates of transmission between different population subgroups through a WAIFW matrix, often stratified by age.

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