Guidance for using modelling for immunization decision-making

World Health Organization

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The lead writers for this guidance were: Alyssa Sbarra (Johns Hopkins University, United States of America), So Yoon Sim (WHO headquarters, Switzerland), Sheetal Silal (University of Cape Town, South Africa), and Philipp Lambach (WHO headquarters, Switzerland). Wirichada Pan-Ngum (MORU Mahidol Oxford Tropical Medicine Research Unit, United Kingdom of Great Britain and Northern Ireland) and Jacquie Oliwa (KEMRI-Wellcome Trust, Kenya) conducted relevant research for the guidance.

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Abbreviations

DALY	disability-adjusted life-year
EPI	Expanded Programme on Immunization
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPV	human papillomavirus
IVIR-AC	Immunization and Vaccine Related Implementation Research Advisory Committee
NITAG	national immunization technical advisory group
RITAG	regional immunization technical advisory group
WHO	World Health Organization
WHO CHOICE	WHO Choosing Interventions that are Cost-effective

Glossary

assumption	An input or condition taken as true for modelling purposes, which may not fully reflect real-life complexity.
benefit–cost ratio	The ratio of benefits to costs; a metric commonly used in benefit–cost analysis that evaluates two or more policy options, interventions or programmes in terms of their costs and outcomes in monetary terms.
case fatality ratio	The ratio of number of deaths from a disease to number of cases of the disease.
counterfactual	A scenario representing what has not happened or would not happen.
cross-validation, cross-validity	A type of model comparison that can be used during model validation consisting of testing a model on data excluded from the dataset. This may be the same model with different subsets of data or different sets of parameters.
deterministic	A type of model in which the outcome is determined only by the inputs and not by randomness.
external validity	A type of model comparison that can be used during model validation consisting of comparing model results with the real world.
face validity	A type of model comparison that can be used during model validation consisting of conferring with field experts to evaluate model structure, data sources, assumptions and results.
incremental cost–effectiveness ratio	A metric used in cost–utility analysis to compare two policy options, interventions or programmes that is calculated as the difference in costs divided by the difference in health outcomes between the interventions or programmes. The ratio represents the additional cost required to gain one additional unit of health benefit, such as a life-year gained or a disability-adjusted life-year averted.
internal validity	A type of model comparison that can be used during model validation consisting of checking the accuracy of coding and data analyses.
mathematical model	A representation of a real-world system using mathematical concepts, including equations or formulas.

model fitting or fit	The process of adjusting the parameters of a model so its outputs closely match (or are calibrated to) observed data. This ensures the model accurately represents historical or current conditions before being used for projections or scenario analyses.
model validation	The process of assessing whether a model accurately predicts data that were not used during model fitting by testing the reliability and credibility of the model in different contexts or time periods.
multimodel comparison	A type of model cross-validation that involves comparing the outputs of different models that address the same question or scenario to help identify consistent findings, understand uncertainties, and assess how differences in model structure or assumptions influence results.
parameter	A value used to represent a property in a model (e.g. the rate at which people with an infection recover), such that, when adjusted, the model's result will change.
predictive validity	A measure of how well a model performs in predicting the occurrence of actual empirically observed outcomes.
projection	An estimate of what could happen in the future, based on model assumptions.
scenario	A specific set of assumptions used in the model to estimate what might happen under certain conditions, such as different levels of vaccine coverage or target age groups.
sensitivity analysis	Testing how results change when assumptions or inputs are varied to check the robustness of findings.
SIR model	A model in which the population is divided into people who are susceptible (S), infected (I), or removed or recovered (R), and people in the population move between these different states.
stochastic	A model that will produce a different output (result) each time it is run, introducing randomness.
uncertainty	The degree to which model results might vary because of incomplete knowledge or variability in data.

Executive summary

Modelling insights for immunization decision-making

Mathematical models are tools that simplify real-world situations. They help decision-makers compare the likely impact of implementing a range of policy decisions on disease burden and other outcomes across a population. By simulating how diseases spread and how various immunization approaches might perform under different scenarios, models can inform decisions on when, how and to whom vaccines should be delivered. Models are used to combine available data and other information, make explicit use of assumptions, and test various scenarios to estimate the likely impact of future decisions.

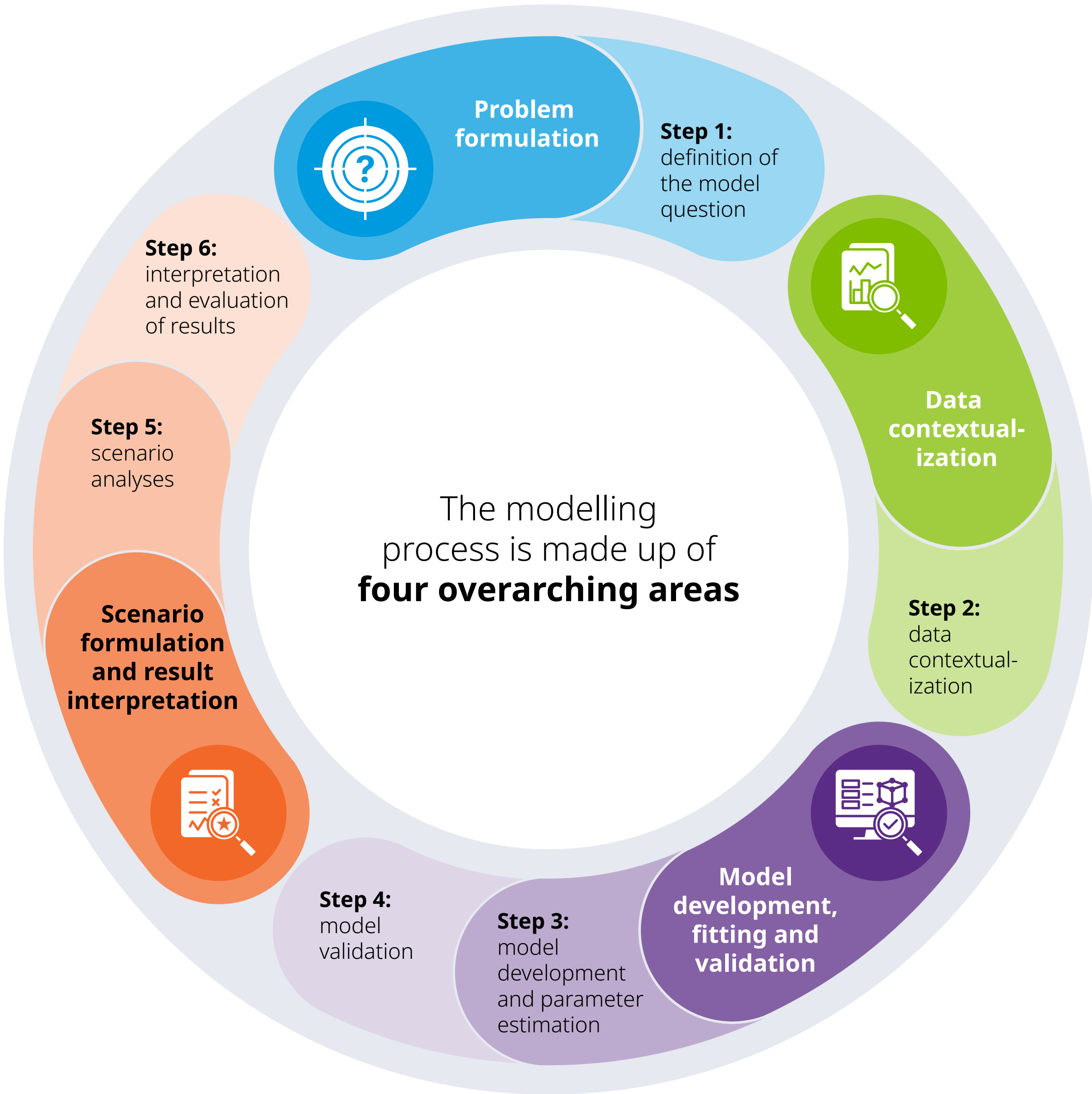
For immunization decision-makers (e.g. national immunization technical advisory group (NITAG) members, regional immunization technical advisory group (RITAG) members, Expanded Programme on Immunization (EPI) managers), these models offer critical insights into outcomes such as the number of illnesses and deaths a vaccine intervention could prevent, the necessary thresholds for achieving herd protection, and the expected costs and economic benefits of an immunization programme. Although models do not replace local evidence, they can bridge gaps in settings where such data are unavailable or incomplete. Ultimately, modelling results should be interpreted in combination with other sources of reliable evidence, operational realities and ethical considerations.

Mathematical models help decision-makers choose strategies that can, for example, save lives or use resources more efficiently, by showing what might happen if certain decisions are made in health programmes. Models are especially useful for vaccine policy decisions because they allow comparison of different programme options using existing data (e.g. vaccination and infection rates, population size, health-care costs). Models can provide critical information, such as predicting the impact of immunization programmes to project how vaccination can reduce numbers of cases, hospitalizations or deaths.

This guidance was developed by the Department of Immunization, Vaccines and Biologicals at the World Health Organization (WHO) and the WHO Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC).

The guidance is designed as a resource to assist stakeholders involved in immunization decision-making – including RITAG and NITAG members, EPI managers, immunization technical working group members, and technical partners who support immunization policy decision-making – in interpreting and applying model estimates. The guidance is based on the findings from a qualitative needs assessment to understand the experiences of immunization decision-makers in using mathematical modelling and feedback from NITAG members and technical partners.

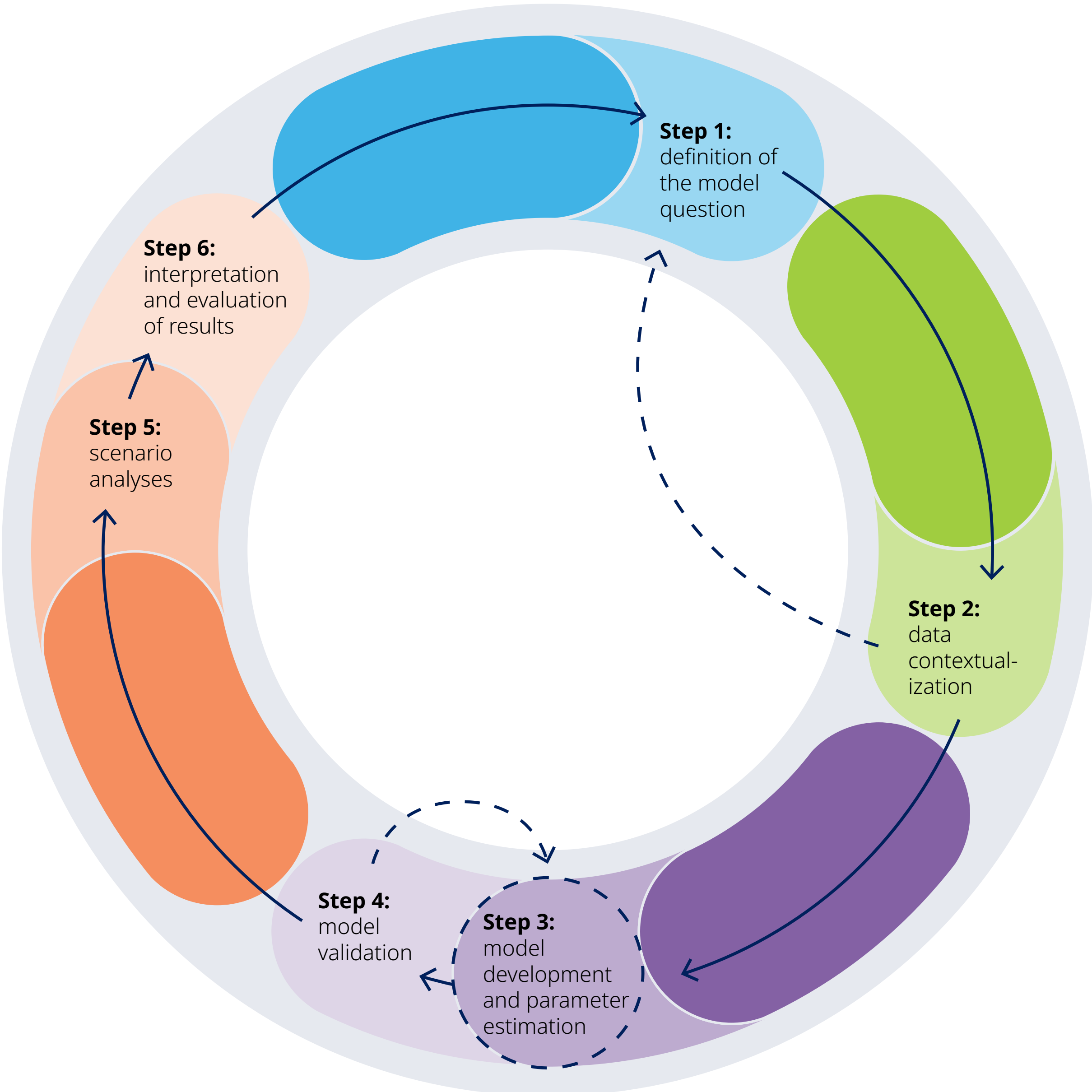
Fig. a. The modelling process



The modelling process

The modelling process is an iterative set of steps mainly consisting of the four overarching areas: problem formulation (including defining the modelling question), data contextualization, model development, fitting and validation, and scenario formulation and results. Model development broadly involves sub-steps including parameter estimation, addressing uncertainty, and model validation. A diverse set of modelling team members, including policy-makers, should be included from the project outset to inform all stages of the modelling process, including defining the modelling question.

Fig. b. The iterative steps of the modelling process



Interpreting and evaluating modelling results

There is no single, “correct” model for all types of policy question, and the appropriateness of a model could be determined primarily based on the question.

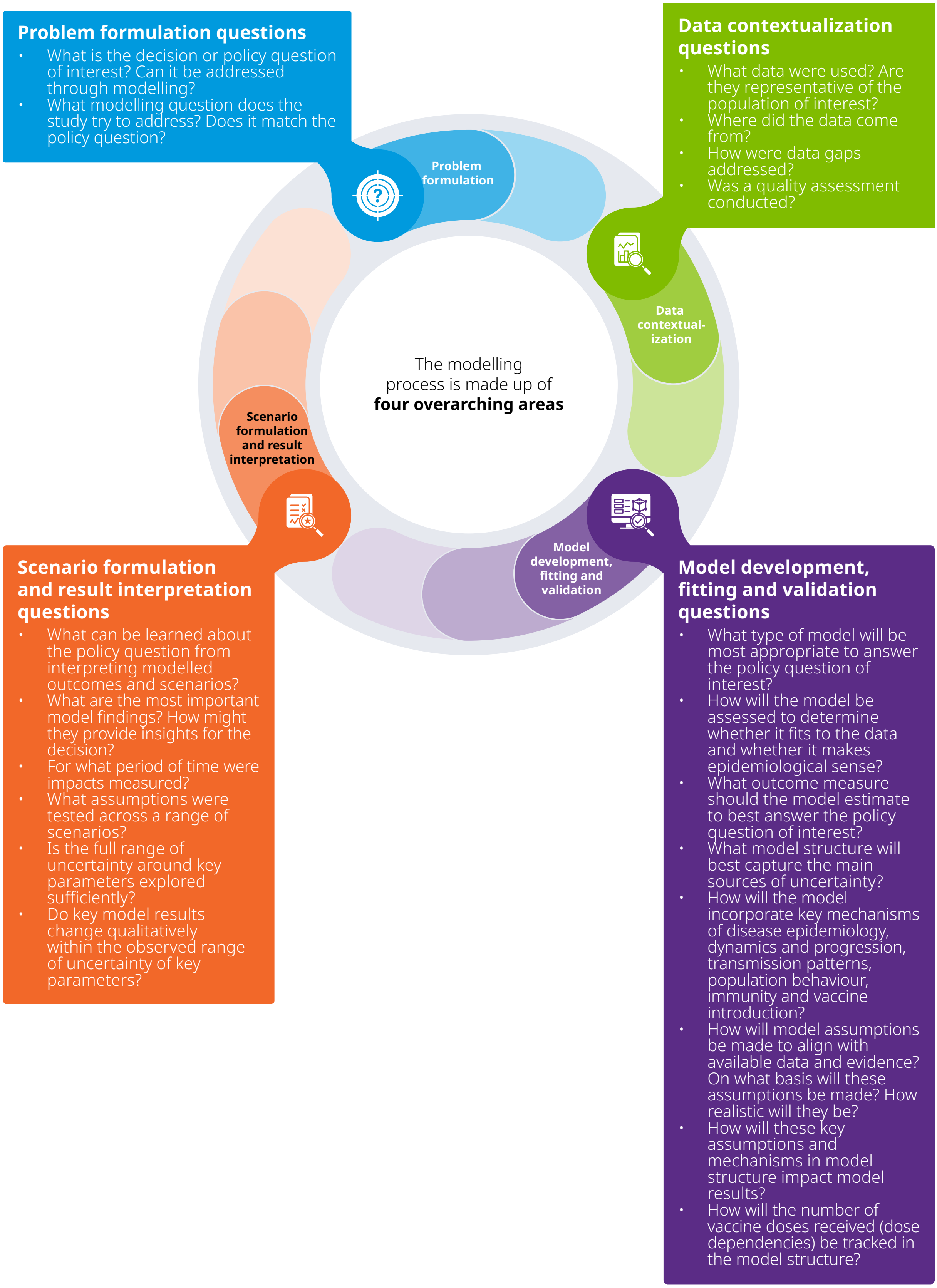
For empirical evidence, we can assess the level of certainty regarding how the true effect is close to the study’s estimated effect. For modelling results, this is not often possible because models produce assumption-based estimates of hypothetical scenarios and do not report observed facts or test scientific hypotheses.

Policy-makers should ensure decisions are well-informed by carefully considering the model’s intent, methodology, assumptions, data sources and sources of uncertainty. If a question cannot be answered through modelling, other research methods may need to be used to answer the question.

In fact, interpreting model results is a process tied to the original questions and assumptions. Modelling outputs may vary based on the geographic, epidemiological and demographic context of the data and assumptions used. Decision-makers should assess whether model outputs answer their specific policy questions and consider the applicability of the findings to their local context. Models inherently rely on assumptions and estimations, and different models may produce different results. All models have limitations, and their outputs carry varying levels of uncertainty. They are not themselves evidence, but rather tools to explore how current decisions may optimally impact possible future outcomes. The usefulness of models relies on quality of the input assumptions and modelled dynamics, and on how closely future conditions relate to assumptions made, which is not known in advance, especially at local scales or over longer timeframes. Models do not report facts but provide a mechanism to support decision-making through exploring the impact decisions made now could have in the future. Despite these limitations, however, models can still be qualitatively informative and help guide decisions when interpreted with care.

Policy-makers should therefore ensure decisions are well-informed by carefully considering the model’s intent, methodology, assumptions, data sources and sources of uncertainty. If a question cannot be answered through modelling, other research methods may need to be used to answer the question.

Fig. c. Overview of modelling process and key questions for engagement throughout the process



Ensuring transparent collaboration

Modelling projects require contributions from multidisciplinary teams, including modellers, epidemiologists, disease or intervention subject matter experts, statisticians, policy-makers, social scientists, programme managers and local health experts. Clear definitions of roles and responsibilities at the outset of the project, strong internal communication and dissemination planning ensure stakeholder engagement and transparency throughout the process.

Conclusion

Mathematical models can support vaccine policy not by supplying verified facts but by providing decision-makers with a structured way to explore plausible scenarios, clarify assumptions, and assess the implications of alternative vaccine strategies. They can be powerful tools to support immunization decisions, particularly when used alongside local knowledge and other decision-support tools. By fostering collaborative engagement, clarifying assumptions and embracing the iterative nature of modelling, stakeholders can better harness these tools to improve health outcomes and inform effective immunization strategies.

Kenya transitions to single-dose HPV vaccine to eliminate cervical cancer- Kilifi, Kenya
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Using modelling for immunization decision-making at a glance

A quick, clickable overview of key parts of the guidance

Background

What is this guidance and why does modelling matter?

This section explains the purpose of the guidance, who it is for, and why mathematical modelling is valuable for immunization decision-making.

See Section 1 ›

About models

What are models and how can they help us?

Here, you will find an introduction to mathematical models, what they can and cannot do, and how they can support the evidence-to-decision process for vaccine policy.

See Executive summary › Section 2 ›

How are models made?

This section outlines the modelling process from defining the model question to gathering data, building and validating the model, and generating scenarios for decision-making.

See Section 4 ›

Models in practice

How can policy-makers and modellers collaborate to use and develop models?

This section explains how effective collaboration, clear roles, respectful engagement and good communication can enable models to support real-world policy needs.

See Section 3 ›

How should modelling results be interpreted and evaluated?

This section provides guidance on judging the relevance, credibility and usefulness of model results by assessing assumptions, uncertainty, data quality and contextual fit.

See Section 5 ›

Tools and resources

Where can I find detailed technical guidance?

The annexes include practical tools for several key parts of the guidance:

- Roles and responsibilities Annex 1 ›
- Model development detail Annex 2 ›
- Understanding uncertainty Annex 3 ›
- Model validation Annex 4 ›
- Scenario analysis Annex 5 ›

1. Introduction

This guidance was developed to facilitate the effective use of mathematical modelling by countries in relation to vaccine-preventable diseases and vaccine use to inform immunization strategies, policies and programme decisions. The guidance is designed as a resource to assist stakeholders involved in immunization decision-making in developing models, interpreting and applying modelling insights.

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The guidance was developed by the Department of Immunization, Vaccines and Biologicals at the World Health Organization (WHO), with input from the WHO Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC). IVIR-AC is an independent advisory group to the Department of Immunization, Vaccines and Biologicals and the Strategic Advisory Group of Experts on Immunization (SAGE) that provides assessment of modelling and implementation science research for immunizations, including to inform global vaccination policy and decision-making.

To aid in the interpretation of model findings for a broader audience, the WHO Secretariat and IVIR-AC established a subgroup to support the translation of modelling to inform immunization strategy, policy and programme decisions, and to advise on communication strategies and guidance for modelling groups *(1)*. The target audience is stakeholders involved in immunization decision-making, including National Immunization Technical Advisory Group (NITAG) members, Expanded Programme on Immunization (EPI) managers, immunization technical working group members, regional immunization technical advisory group (RITAG) members, and technical partners who support immunization policy decision-making.

As the first step, the IVIR-AC subgroup conducted a qualitative needs assessment to understand the experiences of immunization decision-makers in using mathematical modelling *(2)*. WHO Regional Offices supported identifying and recruiting national immunization decision-makers and modellers. The content and format of this guidance were shaped based on findings from the assessment, along with further feedback from NITAG members and technical partners.

An initial scoping review was conducted to identify existing guidance and literature on knowledge translation related to modelling. This review helped identify gaps and informed the normative recommendations.

From 2023 to 2025, a dedicated writing team developed the outline and content of the document, which were reviewed by IVIR-AC subgroup members through four virtual meetings and periodic in-depth review and written comments. Considerations during drafting included feasibility, resource requirements, equity, and alignment with existing WHO policy frameworks.

Three rounds of review sessions were held in June–July 2025 to gather input from Global NITAG Network members, external experts, and colleagues from WHO Headquarters and regional offices. The IVIR-AC full committee reviewed and provided recommendations for the guidance document in September 2025 *(3)*. Additional feedback from modellers was obtained at academic conferences, including Epidemics 9 (28 November–1 December 2023) and Infectious Disease Modelling Conference 2024 (6–8 November 2024).

Feedback from all consultations was synthesized and incorporated into successive drafts of the guidance. To ensure transparency, decisions on content and recommendations were documented. Individuals providing review and input into this guidance are listed in the Acknowledgements section.

Definitions used in the guidance were drawn from literature and existing WHO documents. Where necessary, definitions were developed iteratively through consultation with experts.

Models to inform local decisions are best grounded in local realities. Modelling should use local data as far as possible, which requires established local engagement and leadership throughout the modelling project. Decision-makers also need to interpret and apply modelling insights that were previously generated but not involved in the modelling project from the outset. Under these scenarios, this document provides guidance on how to assess model relevance and utility.

The guidance describes what models are and how they can help in the decision-making process *(Section 2)*; best practices for working together as a modelling team *(Section 3)*; the modelling process *(Section 4)*; and how to evaluate and interpret model results *(Section 5)*. The guidance may be a first-line resource for understanding how mathematical modelling can be used for immunization-related decision-making, but it is only a starting point: users are encouraged to dive deeper into the resources and examples provided.

Joint delivery of malaria vaccines and bed nets, Ethiopia, 2–7 December 2025
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2. What are models and how can they help us?

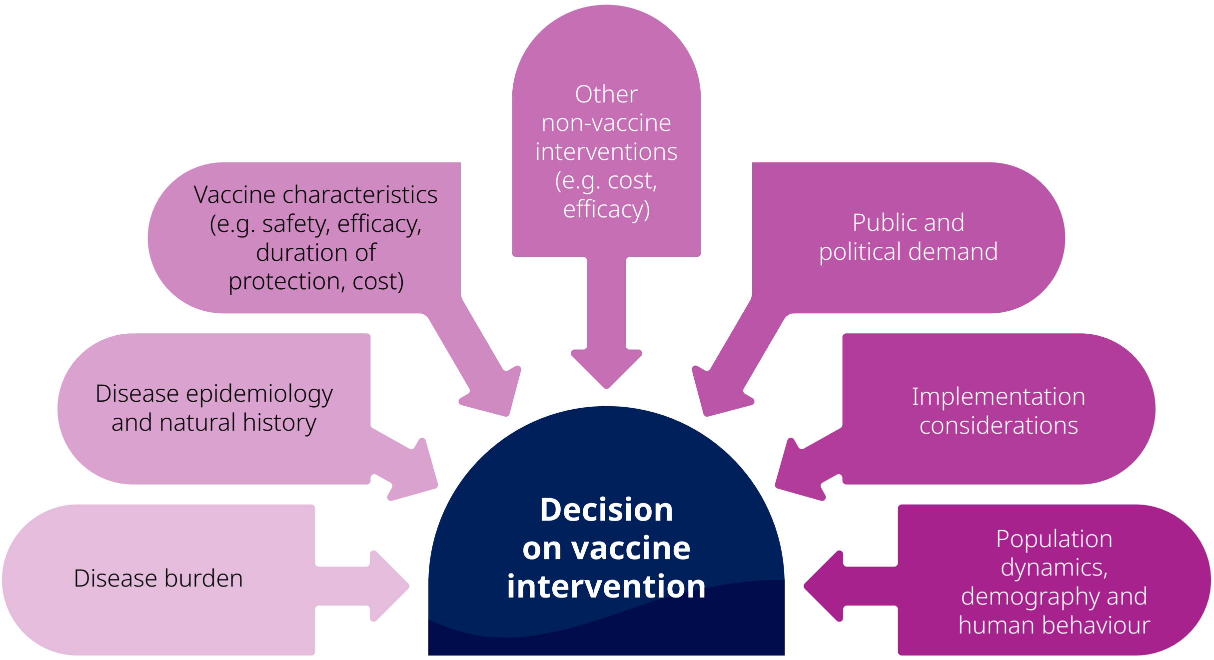
Key messages

- Mathematical models are tools that simplify real-world systems and help us better understand disease patterns and the impact of different vaccination strategies under various scenarios, such as how well different vaccination plans might work depending on when and how vaccines are given.
- Health decision-makers can use models to support their choices about vaccine introductions and policies around vaccine use.
- Models can provide important information, such as how many cases and deaths a vaccine could prevent, the threshold required for herd protection, and the costs and economic benefits of an immunization strategy or programme.
- Models complement – but do not replace – local evidence. Local results, however, may not be available. In either case, decision-makers should use modelling results alongside other types of reliable evidence and operational realities to inform decisions.
- Models allow for extrapolation beyond a clinical study follow-up period, generalizability across settings, and estimation of clinical endpoints from intermediate outcomes.
- Mathematical models may not always be necessary or appropriate to answer a specific policy question.
- Modelling results may be presented in different formats from a variety of settings, such as epidemiological settings, urban or rural settings, or geographical areas.

It is not possible to know the future impact of immunization strategies before their implementation. Mathematical models can help by simulating or replicating the real-world implementation on a computer. Models can then virtually test different implementation strategies and estimate their future impact at a fraction of the cost and time compared with field-based approaches (e.g. randomized controlled trials) or maintaining the status quo.

Mathematical models are a key source of information for global, regional or national immunization decision-makers *(Figure 1)*. This guidance is designed as a resource to assist immunization policy- and decision-makers to understand how to participate in model building, interpret results from mathematical models, use modelling results in the decision-making process, and use best practices when working with modelling teams.

Fig. 1. Considerations involved in choosing a vaccine intervention



2.1 What are mathematical models and what types of model exist?

In health, models can simulate how diseases spread and can estimate the impact of interventions such as vaccination programmes. Models help decision-makers explore possible future scenarios, compare options, and understand the potential benefits and costs of their choices. Based on the policy or research question, these future scenarios may include different vaccine introductions, alternative vaccines and different target age groups. Additionally, models can explore different epidemiological scenarios, such as settings with low or high disease burden or with seasonal trends.

Models often help decision-makers estimate the potential impact of a given vaccination policy on health burden, such as disease incidence, number of hospitalizations, number of deaths or costs. Mathematical models represent these dynamics by characterizing the relationship between potential actions and the outcomes of these actions. These outcomes could include reductions in disease-specific incidence or mortality.

Models also help quantify assumptions, such as the degree of vaccine uptake needed to achieve a desired outcome. Policy-makers can then evaluate, based on other prior knowledge, whether those assumed thresholds are inherently realistically achievable.

Although this guidance focuses on mathematical models that aim to inform policies, models can also be developed to answer scientific questions – for example, exploring the mechanism of action of a vaccine or immune protection from a disease. Insights from these models can be valuable for decision-makers.

Some types of model, such as multivariable statistical models, can be used to determine associations between potential risk factors and outcomes. These models can also be useful for evaluating vaccination programmes. This guidance focuses on mathematical models for performing prospective analyses and simulations.

Statistical models versus mathematical models: what is the difference?

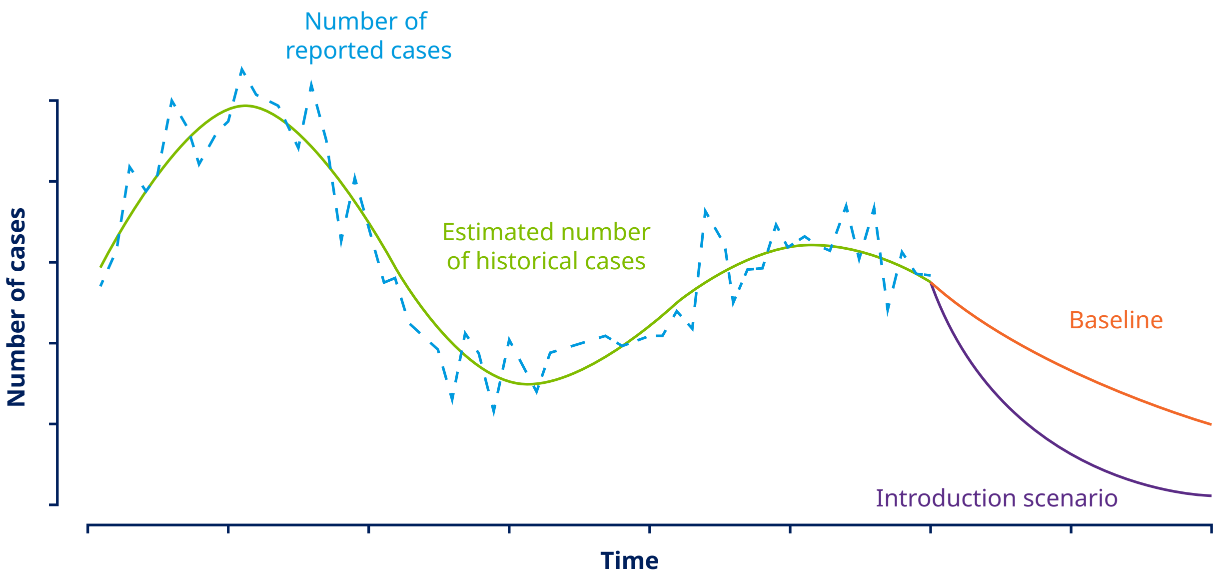
The key difference between statistical and mathematical models is that mathematical models incorporate transmission dynamics and simulation. Statistical models describe past empirical evidence and can be used to forecast short term trends in data, whereas mathematical models can additionally estimate the impact of long term future scenarios on the basis of given assumptions.

2.2 How can mathematical models help us?

By comparing different scenarios, mathematical models help decision-makers choose strategies that can, for example, save lives or use resources more efficiently. An example is shown in *Figure 2*, where a model is fit to a historical time series of cases. Models can show what might happen if certain decisions in health programmes are made, such as introducing a new vaccine or switching the type of vaccine (e.g. the live oral polio vaccine to the inactivated polio vaccine) in different country contexts. *Figure 2* shows two different scenarios – a scenario in which a vaccine is introduced, and a baseline scenario in which no vaccine is introduced. The model predicts outcomes, such as how many people could be protected from illness or how much a programme might cost under certain assumptions. This is especially useful for vaccine policy decisions, because models allow comparisons of different programme options using existing data without the need for large, often impractical and expensive real-world trials.

Mathematical models help decision-makers choose strategies that can, for example, save lives or use resources more efficiently.

Fig. 2. Mathematical model fit to a historic time series of reported and estimated cases, with a baseline scenario and a vaccination introduction scenario



Models use data from the past and assumptions about the future such as vaccination rates, infection rates, population size, effect size of a proposed intervention, and health-care costs to estimate the possible outcomes of different scenarios. Examples of how models can provide critical information include:

- **estimating current and future disease burden** – for example, to understand how many people will be affected by a disease without immunization;
- **predicting the impact of immunization programmes** – for example, to project how vaccination might reduce numbers of cases, hospitalizations or deaths;
- **comparing different immunization strategies** – for example, to assess the relative benefits, risks and costs of targeting different populations, using different schedules or introducing new vaccines;
- **exploring uncertainties and assumptions** – for example, to evaluate how changes in factors such as vaccine efficacy, coverage or pathogen transmission affect outcomes (unrealistic assumptions make desired outcomes unachievable);
- **supporting policy and programmatic decisions** – for example, to provide insights and projections to guide choices about introducing, scaling up or optimizing immunization interventions.

Mathematical models may not always be necessary or appropriate to answer a specific policy question. To determine whether mathematical models should be used, consider the following questions:

- Is a mathematical model necessary, or:
  - can an alternative statistical analysis be conducted?
  - are data available (e.g. from a field study) that already answer the policy question?
- Are there enough data to be able to answer this policy question given the local context?
- Is there enough time to conduct a modelling analysis?

2.3 Who uses mathematical models?

Mathematical models are playing increasingly important roles informing immunization strategies, policies and programmatic decisions. At the global level, modelling is a critical element in the overall policy review process for global recommendations made by SAGE. Global partners identify opportunities for mathematical models before SAGE provides an overall policy recommendation.

Human papillomavirus (HPV) immunization policy recommendations

The following are examples of HPV immunization policy recommendations that were supported by mathematical models:

- WHO position on one-dose HPV vaccination *(4)*;
- HPV policy recommendations in the United Kingdom of Great Britain and Northern Ireland, including one-dose vaccination *(5)* and vaccination of boys *(6)*;
- HPV vaccine introductions in Brazil, Colombia and Poland *(7)*.

At the country level, mathematical models are increasingly used to generate predictive information for decision-making. Models can be used as part of national decision-making before a policy is made and can also confirm the appropriateness of a decision or suggest revisions. Across settings, RITAGs and NITAGs, with input from EPI managers, review model estimates from local and global data and modelling studies, where available.

How might the immunization decision-making process work in a country?

Although there is heterogeneity across countries and vaccines over time, the overall process is standard:

- Global advisory bodies such as SAGE may recommend the introduction of a new vaccine or a change in vaccination delivery or schedule. These recommendations are typically based on a combination of empirical evidence, programmatic data, and modelling results.
- The RITAG or NITAG evaluates available information, including empirical data and evidence and, where relevant, modelling to consider the global recommendations in light of the country or regional context and needs. The NITAG takes implementation considerations into account. If evidence supports a change in the current intervention strategy (e.g. introduction of a new vaccine or a change in vaccination delivery), the NITAG writes and issues a recommendation.
- While the NITAG provides recommendations and advice, the ministry of health typically makes the final decision on implementation and determines the financing options.

2.4 Immunization decision-making process

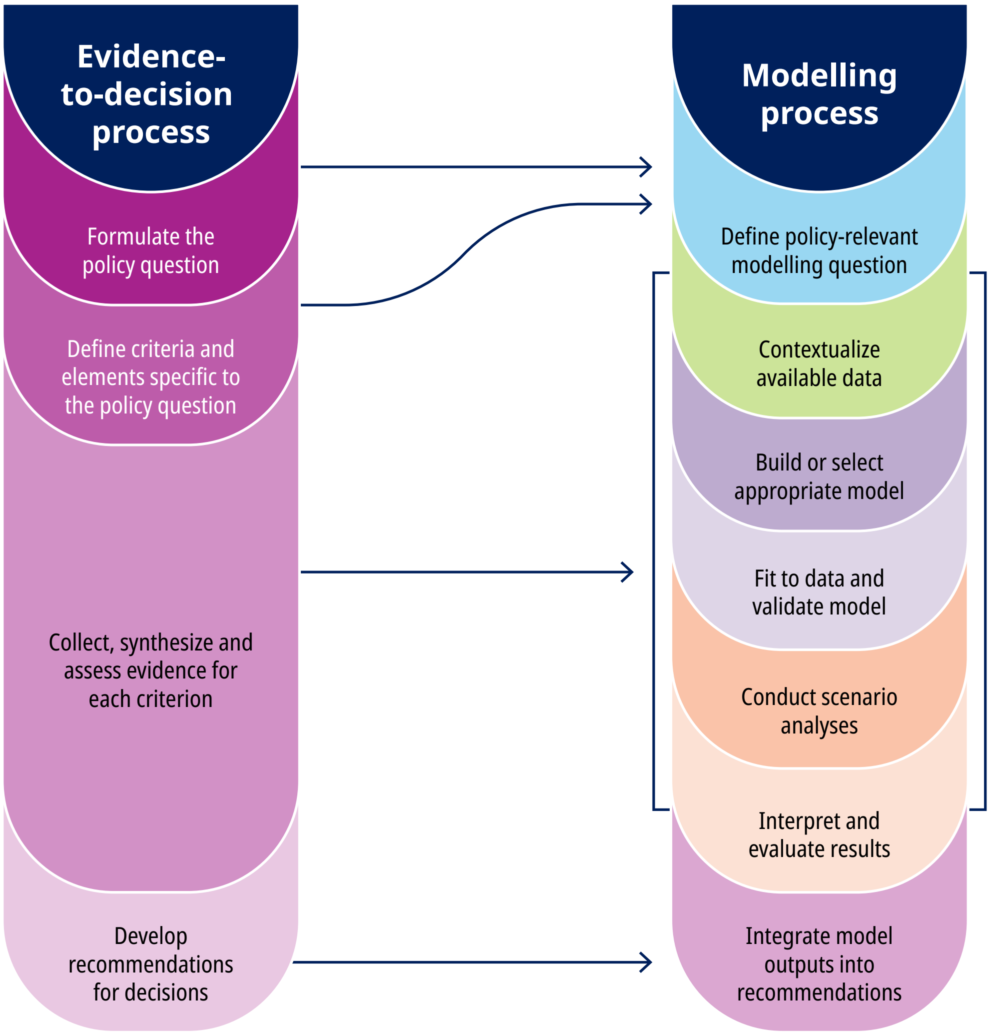
The immunization decision-making process involves several critical steps to ensure recommendations are based on robust and comprehensive evidence. The standard evidence-to-decision process is an example of a policy recommendation framework used by SAGE, RITAGs and NITAGs *(8, 9)*. The evidence-to-decision framework is a structured approach that guides decision-makers through the assessment and appraisal of evidence and contains the following elements *(Figure 3)*: background information and the research question; specific criteria to consider and the related judgements made for each criterion; research evidence to support each judgement; and additional information to justify the judgements and decisions made for each criterion (i.e. problem statement, benefits and harms of the options, certainty of the evidence, values and preferences, resource use, equity, acceptability and feasibility). The evidence-to-decision framework concludes with the balance of consequences of benefits and harms, the recommendation and justification for it, implementation considerations, and research priorities.

The *WHO guide for evidence-informed decision-making* presents several frameworks to support the use of evidence in policy processes. One of these frameworks – the evidence creation funnel *(10)* – outlines the stages involved in finding, synthesizing and applying evidence to inform decision-making. The evidence creation funnel comprises three processes: evidence inquiry (primary research), evidence synthesis (secondary research), and evidence products (tertiary research). Within this framework, modelling fits within the evidence synthesis stage, as it draws on findings of individual research studies and broader bodies of evidence to generate insights based on what is known to date and identify remaining evidence gaps.

The evidence-to-decision process starts with formulation of a clear policy question based on the population of interest, intervention, comparator and outcome. The modelling question can be adapted from the policy question *(see Section 4)*. Examples of modelling questions include:

- "Should two doses of an HPV vaccine be given to girls aged 9–14 years to reduce HPV infections and HPV-associated cancers?"—Standing Committee on Vaccination, Germany, 2014.
- "Should we change the HPV vaccination schedule from two doses to one dose in the routine adolescent programme for children and young people age up to and including 14 years of age?"—Joint Committee on Vaccination and Immunisation, United Kingdom, 2022.

Fig. 3. Evidence-to-decision process and related modelling project phases



The evidence-to-decision process guides the collection of evidence. During the data collection phase, decision-makers may consider different types of evidence, including:

- randomized controlled trials;
- observational data, mainly from vaccine effectiveness and safety studies;
- outbreak investigation reports;
- post-market disease or vaccine surveillance studies;
- programme evaluations;
- disease or vaccination impact modelling;
- cost–effectiveness evaluations;
- global market dynamics and supply estimates;
- qualitative data on values, preferences, equity and acceptability.

Modelling is particularly useful when:

- the overall population level impact of a vaccine programme has not been captured in the available studies – for example, the available clinical trial data may show only direct individual-level protection in people who are vaccinated but not measure indirect herd protection effects;

- there is uncertainty about vaccine characteristics or virus evolution (e.g. SARS-CoV-2);
- there is a need to explore multiple hypothetical scenarios about different vaccination strategies;
- there is a need to compare scenarios with counterfactuals that cannot be evaluated in real-world settings (e.g. comparing dosing scenarios of routinely used vaccines with the counterfactual of no vaccination);
- incomplete and insufficient surveillance data are available;
- impact can be expected only several decades in the future.

Decision-makers have several options for obtaining the necessary modelling insights:

- Develop or commission new models: internal teams co-develop models with external modelling groups or commission modelling work solely to external modelling groups to answer a specific policy question. This is an ideal modelling process that encourages co-creation and local capacity strengthening *(see Sections 3 and 4)*.
- Gather existing modelling studies: review existing studies through systematic literature searches for previously published models and pool the results found *(see Section 5)*.

Each of these approaches requires the model input and assumptions to be tailored to the specific context and needs of the decision-making process.

For trials, observational studies and systematic reviews, the quality and certainty of the evidence are assessed using criteria such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework based on study designs *(11)*. It is important to note, however, that there is currently a lack of standardized criteria for evaluating model estimates. This guidance, therefore, aims to equip decision-makers with the necessary tools to critically appraise model estimates, while accounting explicitly for underlying assumptions and uncertainty.

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2.5 Modelling and economic evaluations

Economic evaluations are a key component of immunization decision-making, helping assess resource use and allocation under various scenarios.

Economic evaluations integrate outcomes from mathematical models with costs, depending on the choice of perspective for the evaluation – such as costs for the health sector or costs for patients and their families, including lost productivity – to support resource allocation decisions. Common approaches include cost–effectiveness analysis, cost–utility analysis and cost–benefit/benefit–cost analysis, each measuring outcomes differently based on disparate theoretical foundations. Advanced methods such as extended cost–effectiveness analysis and distributional cost–effectiveness analysis aim to address equity concerns by quantifying the distribution of costs and health outcomes across sociodemographic variables such as socioeconomic status, location, ethnicity, sex and severity of illness *(12)*.

Mathematical modelling underpins economic evaluations by inferring attributable clinical burden from existing data through the natural history of illness and estimating the disease burden of an infectious disease and impact of vaccination on the disease burden. As such, economic evaluations often incorporate model-derived disease burden and impact estimates, which should be assessed using the same principles outlined in this guidance. If results from mathematical modelling and economic evaluations are prepared separately, cross-validation is recommended to appraise disease burden and impact estimates.

The *WHO guide for standardization of economic evaluations of immunization programmes, 2nd edition* provides practical guidance on how to conduct economic evaluations *(13)*. The WHO Choosing Interventions that are Cost-effective (WHO-CHOICE) initiative provides guidance on conducting cost-effectiveness analyses to assess the efficiency of a health system and support decision-making on new interventions *(14)*. These resources are updated periodically to reflect emerging insights and best practices.

2.6 Different sources of model estimates

Model estimates may be presented from different sources, depending on the original intent. The results may have been generated for a central international or local advisory body, such as the RITAG or NITAG or SAGE. Alternatively, model estimates may come from an independent publication, perhaps from a different country or region, which may or may not be similar to the setting of interest. The model estimates could also come from a bespoke modelling study conducted for or in the local setting of interest, with or without participation of the modelling team *(see Section 3)*.

Regardless of the format of the modelling insights, the suitability of the modelling insights to the decision must be considered. The means for addressing the suitability for each type of results may need to be tailored specifically to the specific local policy-related decision.

2.7 Recommendations and policy decisions

A policy decision or recommendation should be based on a balanced assessment of all relevant benefits and harms. To ensure transparency, decision-makers are encouraged to document the process thoroughly and to communicate clearly to key stakeholders – including modellers, when involved – how modelling contributed to shaping the final recommendation. For further information, see *Section 5*.

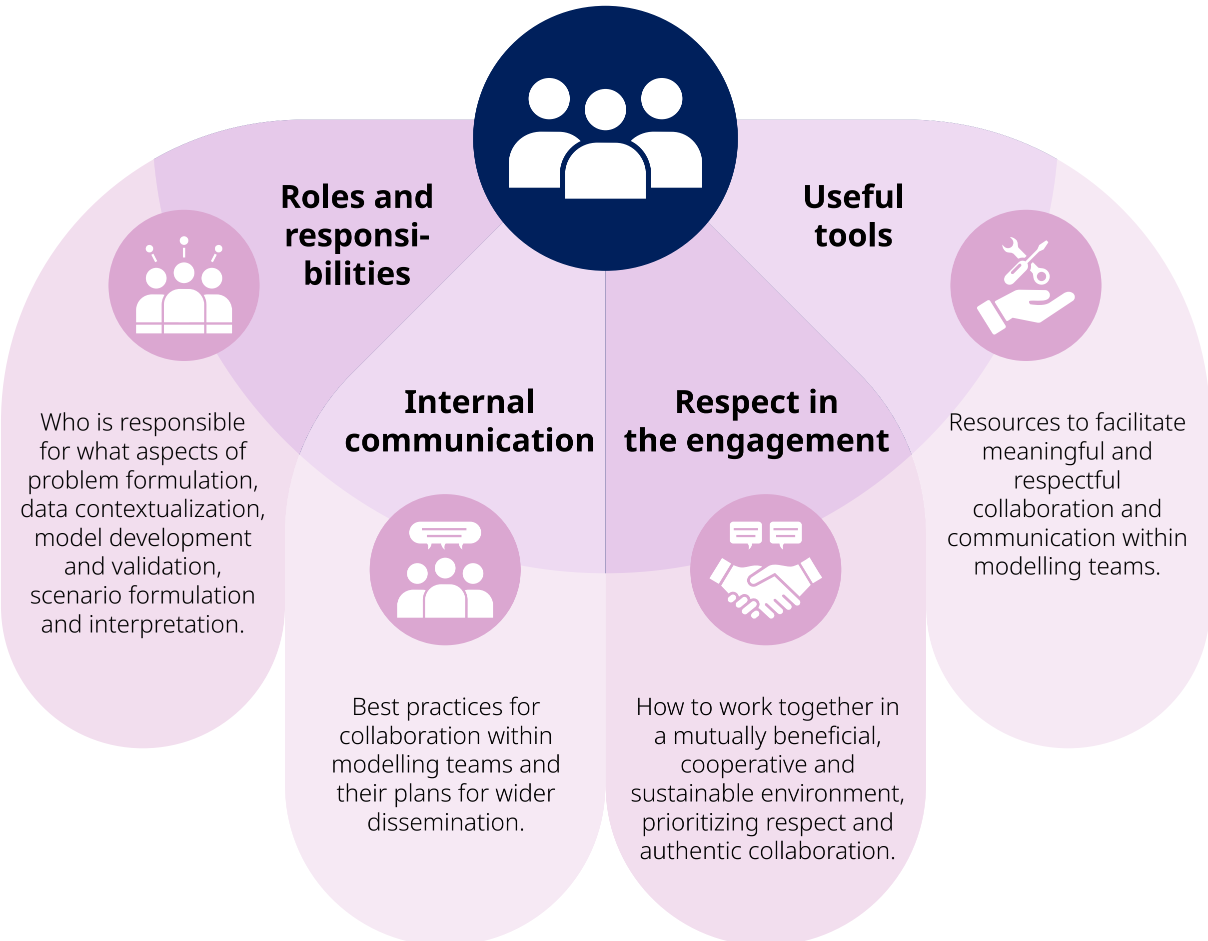
3. How can policy-makers work together with modellers?

Key messages

- People from many diverse backgrounds and roles make up a successful modelling team. Defining roles and responsibilities at the outset for each stage of the project – including the early involvement of end-users – helps to facilitate a successful collaboration and ensures models address practical decision-making needs.
- Establishing internal communication and plans for wider dissemination helps to foster clear expectations and respect among project team members. Respect in the engagement is critical to the success of the modelling project and should be prioritized.
- Multiple tools are available for modelling teams to facilitate successful projects and guide longstanding collaborations.

Overall, the impact of modelling exercises and projects depends on the success of the engagement of all relevant stakeholders. This is a critical component to prioritize alongside the rigour of the modelling. *Figure 4* lists the collaboration and engagement factors that should be taken into account:

Fig. 4. Collaboration and engagement factors



3.1 Roles and responsibilities

Modelling projects involve many people with diverse expertise, including decision-makers, public health officials supporting decision-makers, advisory bodies (e.g. RITAGs, NITAGs, SAGE), the general public, vaccine manufacturers, disease specialists and local implementers. Each person has an important, different but complementary role to play, bringing unique perspectives on different components of the modelling process.

A modelling project may be initiated in multiple ways, such as by a country immunization programme, a WHO regional or country office, WHO Headquarters, country partners (including NITAGs), other stakeholders (e.g. nongovernmental organizations, funding agencies) or modelling groups. The first step of initiating a modelling project is to align priorities across partners. The roles and responsibilities of members of the specified project team are then aligned *(see Annex 1)*. Modellers should engage with the RITAG and NITAG directly to identify modelling questions, collaborate on collecting, reviewing and using data, and discuss how results can be applied in local contexts. This work occurs in an iterative process over the course of the modelling project, from formulating the project to interpreting and disseminating results. Advisory bodies such as SAGE may help to identify data sources and provide an independent review of the methods or results. Disease specialists, vaccine experts, vaccine manufacturers or other relevant local experts may provide insight into specific aspects of pertinent biological, immunological or epidemiological phenomena and data sources.

Each member of the modelling project team has a specific role to play at each stage of the modelling process. For example, advisory bodies may set overall research priorities, while local decision-makers and modellers may co-define specific policy questions and determine how to translate these questions into quantitative models. At the outset of the modelling project, determining team members and their respective roles and responsibilities will make for a more successful engagement. Overall, members of the public should provide feedback, likely via implementers such as EPI managers, on the policy question on priorities and acceptability of proposed scenarios.

Ideally, modelling projects should involve decision-makers and a diverse collaborative team from the outset, but this may not always be the case – for example, if an academic group publishes a mathematical model with disease burden estimates in a peer-reviewed journal, which decision-makers or implementers discover later. Many roles, responsibilities and key considerations for model evaluation remain consistent, including evaluating the appropriateness of the model structure and assumptions to answer the policy question; understanding the generalizability of the model to local settings; and interpreting the model results, limitations and uncertainty.

3.2 Internal communication

Communicating modelling methods and results within the project team is critical for the success of modelling engagement *(2)*. When communicating modelling methods, best practices should be used, including iterative discussions of modelling assumptions and scenarios throughout the model development process. Code should be shared internally and externally in an open-access repository. Data should be shared within the project team as freely as ownership and data-use agreements permit.

Internal communication within the project team is important to ensure the success of the engagement process. Key components of good communication practices include:

- setting up channels for simple and direct communication and messages (e.g. email, other messaging platforms);
- scheduling regular meetings with relevant team members, and identifying any key goal dates for the project timeline;
- if possible, planning and attending in-person meetings throughout the duration of the project.

3.3 Respect in the engagement

The success of the modelling project hinges on the success of the engagement, which is critically dependent on underlying respect in collaboration *(15–17)*. Respect, which includes but is not limited to underlying ethical considerations, is necessary across multiple aspects of the project, from problem formulation to interpretation and dissemination of results. Modelling projects should be beneficial for all team members, promote cooperation and authentic collaboration, encourage best practice data-sharing, and lead to sustainable collaboration and capacity-building. The following components should be considered before embarking on a modelling project.

3.3.1 Structural aspects of engagement

Decision-maker engagement should be embedded throughout the whole modelling project, including in the design process and later during utilization. From the start of the project, development of structural procedures, including defining appropriate roles and responsibilities and identifying key timepoints for stakeholder engagement, should be conducted with respect. It is important to establish leadership structures that include local experts, and to have local representatives leading the processes to define the project objectives and realistic modelling scenarios. A principal member of the team (e.g. a government champion for the project), who will be responsible for receiving communication from modellers, should be established to develop the communication protocol. Establishing agreed timelines for the data-gathering, modelling, engagement, communication and dissemination plans is essential for the success of the project and harmony within the project team. It is critical that everyone in the modelling team has access to the results. From the outset of the project, there should be agreement over which team members, prioritizing local expertise, will lead the communication and dissemination of results.

These steps are an ideal structure of engagement. Realistically, however, they may not all be possible or feasible in a specific context, and they should be evaluated on a project-specific basis.

Additional resources

Noor AM. Country ownership in global health. PLOS Glob Public Health. 2022;2(2):e0000113. https://doi.org/10.1371/journal.pgph.0000113.

- This outlines key components related to country ownership, including understanding roles across research partners.

Silal S, Bardsley C, Menon R, Abullahi L, White L. Epidemiological modelling for public health decision-making in sub-Saharan Africa: a strategic plan for capacity strengthening. London: Foreign, Commonwealth and Development Office; 2022 (https://www.opml.co.uk/files/Projects/a4964-epidem-modelling-capacity-strengthening.pdf).

- This explores requirements for strengthening national-level capacity of researchers and policy-makers, examines case studies in the African Region, and provides a conceptual framework to develop capacity-strengthening strategies.

Full report: guidance on use of modelling for policy responses to COVID-19. Nonthaburi, Thailand: Health Intervention and Technology Assessment Program Foundation; 2020 (https://www.hitap.net/en/document/covid19-policy-modelling-guidance/).

- This offers overall guidance on modelling for decision-makers and highlights collaboration with in-country partners.

Guidance for country-level TB modelling. Geneva: World Health Organization; 2018 (https://iris.who.int/handle/10665/274279. License: CC BY-NC-SA 3.0 IGO).

- This provides principles and good practices, with a focus on country ownership.

Working with partners. Applied Malaria Modeling Network (AMMnet); 2025 (https://www.ammnet.org/resources/working-with-partners).

- This webpage presents best practices in engaging with national malaria control programmes to build trusting relationships and strengthen capacity from a modeller's perspective.

3.3.2 Ethical considerations

Ethical considerations in modelling projects include ownership of data and results *(18)*. (See the box "Additional resources" for more information.) Acknowledging and respecting practice best data-sharing, including potential local data ownership, is critical for successful engagement. To protect local data, it may be necessary to adapt a memorandum of understanding or agreement or a data-use agreement *(see Section 3.4)*. Ownership of results should be discussed early in the planning stages of the project and should always prioritize respect for local ownership. Ownership of the models should also be discussed. These discussions should consider who has intellectual property rights for the models and the preferred mode of future engagement for maintenance and follow-up, including the need for future resources.

Additional considerations include capacity-building and opportunities for learning. Local skills should be leveraged whenever possible. Members of modelling teams are frequently not from the local setting, however, due to the skilled training and computational infrastructure required for modelling. If there is interest from local experts, modellers within teams should take the opportunities within a project to promote capacity-building and opportunities for learning through hands-on and applied experiences within the project.

Additionally, since modelling is not commonly used by many local and regional advisory bodies such as RITAGS and NITAGs, it is important to increase the capacity of these groups to interpret and critically appraise modelling insights with support, including through this guidance document.

If conducted responsibly, modelling facilitates explicitness and transparency, which itself contributes to ethical policy development.

If conducted responsibly, modelling facilitates explicitness and transparency, which itself contributes to ethical policy development. Overinterpretation and inferences that are insufficiently supported, however, can lead to suboptimal policy; therefore, understanding and communicating modelling limitations also has ethical implications. Ethical considerations are also needed when preparing model inputs – for example, when planning a specific subgroup analysis, or incorporating distributional questions, disaggregated data representative of these populations should be prioritized for inclusion.

3.3.3 Writing and sharing results

Dissemination is a critical component to modelling projects. This dissemination should include not only model results but also model limitations and limitations of interpretation of the results. Written reports or publications are often shared broadly, including with local communities. To ensure accessibility, project teams should write short summaries using clear phrases and direct language. Translations should be made available in the languages and dialects of the key stakeholders, when possible and applicable. Writers should provide useful open-source references and should prioritize citing local authors, when available and appropriate.

All project team members should contribute towards preparing materials for policy-makers, the media and the general public, as appropriate. This may include preparing media packs or policy briefs with specific information targeted for relevant stakeholders.

3.3.4 Creating a feedback loop

The decision-makers are responsible for sharing with the modelling team how the modelling results were used in their decision-making processes and what the outcomes were (e.g. a new vaccine was recommended or a policy was adapted). Modelling teams can learn from the experience of how the results were used and perceived during the decision-making process. This also helps to facilitate timely completion of project timelines.

3.3.5 Responsible modelling

Modelling is not only a technical process. It also involves value judgements from decision-makers and modellers. Responsible modelling integrates ethical considerations to ensure models are trustworthy, equitable and useful for decision-making. The Lancet Commission for Strengthening the Use of Epidemiological Modelling of Emerging and Pandemic Infectious Diseases proposes key ethical principles and actions to which modellers should adhere to enable responsible modelling *(19)*. Decision-makers could use this tool to assess ethical considerations of modelling, such as:

- **Beneficence/non-maleficence**: are models used to promote good and avoid harms?
- **Justice/equity**: are models used to address distributional impacts and strive for fairness?
- **Integrity**: are assumptions, limitations and funding sources communicated transparently to the general public?

Models should serve as advisory tools. Decision-makers should retain clear accountability for decisions informed by models and other relevant evidence. When decision-makers are accountable to people, they are responsible for providing justifications for their policy decisions and the supporting evidence underpinning their decisions. Decision-makers can involve the general public more closely in the modelling process to account for diverse perspectives and increase public trust. Modellers assume responsibility by adhering to professional standards and ethical codes of conduct in research. Given the social dimension of value judgements embedded in the model, it is critical to ensure diversity of models and perspectives to reduce systematic bias.

To increase transparency about underlying assumptions, every model should have public documentation tailored to the level of expertise of any interested audience *(20)*. Non-technical documentation should be available to all who request it. Technical documentation can be made available openly or under agreements that protect intellectual property. The increasing importance of transparency and accountability of models and their deployers is evidenced in the “right to explanation” under legal safeguards. An example of these legal safeguards, particularly relevant to models or analyses relying on artificial intelligence, is the European Union Artificial Intelligence Act, which was designed to ensure a person’s right to receive clear and meaningful explanation of the role of artificial intelligence in the decision-making process.

3.4 Tools to facilitate successful engagements

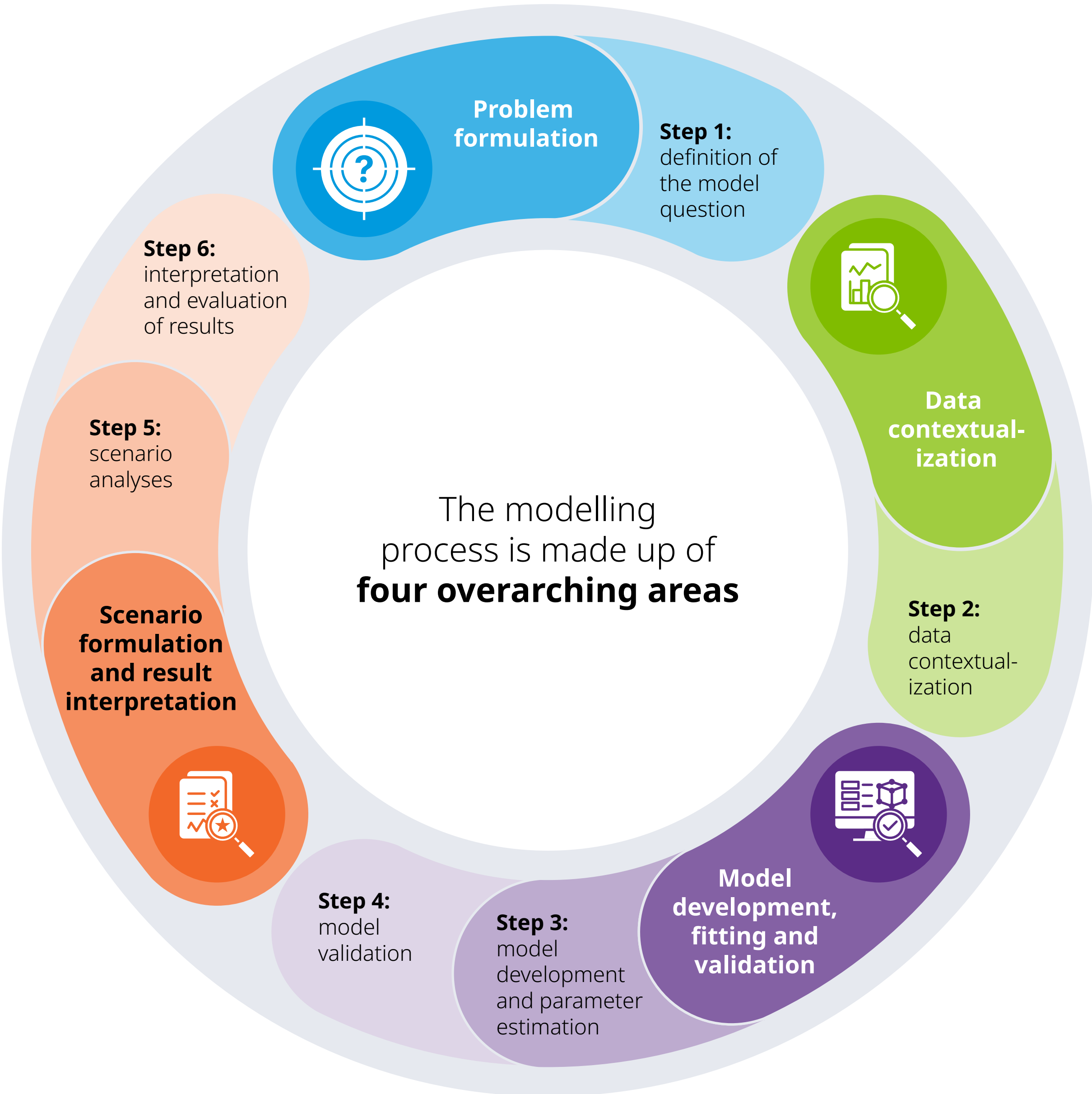
Many successful engagements have relied on existing tools and frameworks to facilitate productive and successful modelling collaborations. Although specific tools may be helpful at different stages of the project, most tools are best established at the project outset. The following tools and engagement platforms may help to facilitate future or ongoing modelling projects:

- Lancet Commission for Strengthening the Use of Epidemiological Modelling of Emerging and Pandemic Infectious Diseases *(19)*:
  - **Purpose**: to guide project scoping and to define modelling objectives.
- WHO Collaboratory *(21)*:
  - **Purpose**: to provide space to address key challenges related to data for pandemic and epidemic policy- and decision-making.
  - **Components**: community member discussions, resources and collaboration opportunities.
- Memoranda of agreement:
  - **Purpose**: to manage key aspects of data-sharing and modelling expectations, permissions and collaborations.
  - **Components**: signed, legal documentation outlining parameters of agreements for collaboration, sharing and ownership.
  - **Resources**: discuss specific templates with local data and/or human subjects departments, such as the institutional review board.
- Progress monitoring via key meetings:
  - **Purpose**: to align key project personnel on project happenings, and to keep the project on time and on task.
  - **Components**: in-person or online meetings scheduled at key milestone intervals of the project.

4. How are models made?

Key messages

- There are six main steps in the modelling process, including defining the model question, contextualizing the data, developing the model and estimating parameters, validating the model, constructing scenario analyses, and interpreting and evaluating results.
- The modelling process is iterative and requires input from many partners, including local experts, modellers, policy-makers, epidemiologists and statisticians.



Mathematical models can show how vaccines could change the transmission or severity of disease compared with the status quo or across multiple implementation strategies. These models allow exploration of "what if?" scenarios based on key assumptions, which can help guide decisions about public health actions when we do not have all the required real-world data or cannot test all scenarios of interest. This section provides guidance for people who use outputs from models, such as public health officials and immunization decision-makers, on how to formulate clear questions for modelling, collect data, understand how models are produced, and support the modelling process.

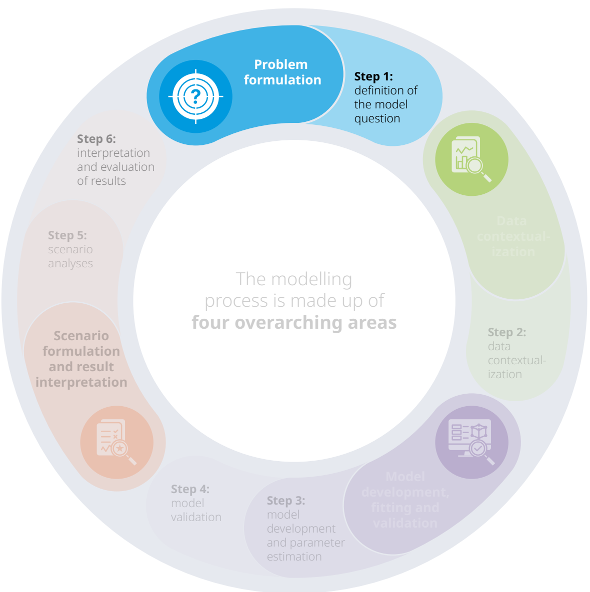
4.1 Developing a model

Creating a model for decision-making is a dynamic, collaborative and iterative process, requiring input from multiple stakeholders at every stage. This process can take time, which should be aligned with the related decision-making cycle. Through this iterative process, with a specific task for each project stage *(Table 1)*, a well-designed model becomes a powerful tool for guiding informed decisions.

Table 1. Tasks for each modelling project phase

Project phase	Task
Problem formulation	Advise on priorities for research and modelling
	Define decision problems
	Translate policy question into quantifiable modelling questions
	Advise on feasibility assessment
	Synthesize knowledge on disease and vaccine/clinical trials
Data contextualization	Conduct an extensive literature review to understand the broader views of similar questions and existing modelling work on the topic in various settings
	Review model structures, assumptions and parameters
	Review roles and dose regimens of vaccines in the model
	Review assumptions about the disease and transmission
	Assess feasibility of vaccine implementation

Project phase	Task
Model development, fitting and validation	Make sure data are parameterized correctly for the model Help identify the sources of data for modelling Review data inputs and data for model validation Review or provide data related to vaccine characteristics and efficacy Review or provide data related to disease characteristics
Scenario formulation and result interpretation	Perform scenario analyses and sensitivity analyses Review scenario formulation and interpretation Assemble model results Provide feedback on the practical points regarding the model scenarios Review vaccine scenario construction and interpretation



4.2 The modelling process

4.2.1 Step 1: define the model question

Model construction begins with defining a clear question based on the policy issue that seeks information in the modelling study. Not all questions can be answered using models, and it is critical to articulate the question such that it can feasibly be addressed.

At the outset of the project, it is essential to define the questions that the model will help to answer. This not only helps to select the right type of model but also ensures that all people involved – including decision-makers, modellers and other partners – are aligned on the goals and understand how the model will support policy decisions.

Decision-makers may consider the value of the information that the results could provide to determine whether modelling is worth the effort and resources. These considerations could include how much better decisions could be made if uncertainty was reduced from the insights provided by modelling results.

Key questions for consideration

- What is the decision or policy question of interest? Can it be addressed through modelling?
- What modelling question does the study try to address? Does it match the policy question?

There are three key sub-steps to defining the problem and setting the modelling question:

4.2.1.1 Clarify the objective of the modelling exercise

The objective of the model should be linked directly to a policy decision. For example, if the decision is about changing a vaccine schedule, the model should focus on predicting how different schedules would affect disease incidence and costs. It is essential to agree on this objective with all partners through open communication.

Models can help answer many questions, but not all – especially when also considering the data available to use in the model. It is important at the outset of the project to understand what types of question models can and cannot answer.

Examples of questions that models can be used to answer include:

- What is the relative difference in malaria burden if a country introduces a new malaria vaccine under different delivery schedules?
- What vaccination strategies would lead to the feasibility of measles elimination?
- Approximately how many people would need to be vaccinated with pneumococcal vaccines to achieve herd protection?

Examples of questions that models cannot be used to answer include:

- What is the exact number of malaria cases that will be averted if a country introduces a new malaria vaccine?
  - This cannot be answered, because models cannot predict with precision exactly what will happen. Models can provide an estimated range of cases given assumptions about what may happen.
- What vaccination scenario will cause measles elimination?
  - This cannot be answered, because there are factors other than the number of predicted cases that determine whether a country has achieved elimination goals (e.g. surveillance standards).

4.2.1.2 Review existing data and information

Before creating a new model, it is helpful to look at existing data and information, including previous modelling studies from global, regional or other country-specific contexts, to provide a baseline understanding of the existing data and results. It is also important, however, to gather information specific to the setting, such as immunity or susceptibility profiles (e.g. serosurveillance), outbreak history and vaccination coverage. Additionally, global, regional, national and subnational considerations should be reviewed, including current global policy recommendations and other regional epidemiological trends.

Understanding which data are available is critical to establishing what inputs are available for modelling. If data are not available, modelling can still be done by making additional assumptions or approximations, but the modelling exercise may be constrained on what it can realistically answer for a given setting. For example, if no setting-specific data are available across multiple sources of data (e.g. data repositories or information collected by ministries of health), a model may not accurately reflect the transmission dynamics of that specific setting. This process may help suggest which data should be collected. *See Section 4.2.2* for more information.

4.2.1.3 Identify outcomes to measure

The outcomes of the model should contribute relevant evidence to inform the decision-making process or to help answer the policy question.

The outcomes of the model should contribute relevant evidence to inform the decision-making process or to help answer the policy question. For example, if the policy question is related to reducing mortality, the modelling question and outcome should focus on evaluating mortality or deaths across different scenarios. Other secondary outcomes may include incidence, prevalence or costs (e.g. costs of implementation versus costs of non-implementation). Depending on the policy question, it may be important for the modelling question and outcomes to include additional specifications (e.g. relevant age groups) or indicate that a specific choice of product is advantageous.

It is important to ensure the model has sufficient but only necessary detail to answer the question of interest. For example, to explore the impact of different vaccine dosing schedules, the model must reflect these schedules realistically with respect to timing, target age group and delivery platform, and a detailed knowledge of the vaccination and disease burden among single age groups (e.g. children aged 1 year, children aged 2 years) may be required. If the model groups together all children aged 1–14 years, then it may not be sufficiently detailed to answer the question.

Balancing sufficient but only necessary details is important and often requires multiple conversations with various stakeholders to consider relevance and appropriateness alongside feasibility and to avoid unnecessary complexity, which can make the model output more difficult to interpret.

HPV vaccination example

Throughout the rest of this document, the following example is used:

A NITAG is required to provide a recommendation on whether the country should introduce an HPV immunization programme – and if so, among which targeted age groups (e.g. children aged 9–10 years, children aged 11–12 years) and by using one dose or two doses.

One of the tools that can be used to provide insights to support this decision-making process is modelling.

The policy question may be: "Should the country vaccinate against HPV, and how is it best implemented?" The part of the policy question that can be evaluated with the help of a model may be: "What will be the health and economic impact of implementing an immunization programme for one dose versus two doses for boys and girls in specific age groups in the country?"

The following checklist may be used to frame the modelling question:

- What health metrics of interest (e.g. cases of cervical cancer, deaths attributable to cervical cancer) are mentioned in the policy question?
- What should be the main contributors (e.g. presence of an at-risk group, vaccine efficacy) to these outcomes in specific contexts, and under what timeframe (the projection period) should results be collected?
- Which vaccine characteristics, such as effectiveness against different outcomes, need to be incorporated into the model assumptions and parameters? This will likely include making assumptions for some parameters for which few empirical data are available (e.g. duration of vaccine protection).
- How will indirect effects of vaccination (e.g. herd protection, serotype replacement or increases in the average age of infection) need to be incorporated into the model?
- How should vaccine introduction be implemented in the model? This may be under different scenarios, including a counterfactual where no vaccine is introduced.
- What features of immunization coverage (e.g. timeliness, number of doses) are important for the model to capture under different scenarios or overall in the model structure?
- How should population-representative demographics be incorporated in the model, including age groups, contact patterns and population growth?
- How can modelling help to inform the decision? Since modelling can provide insights into what may happen in different scenarios under specific assumptions, we can consider what model outputs may be helpful to address the policy question. Policy questions translated into modelling questions frequently compare health outcomes across different modelling scenarios, but they can also include determining thresholds for the number of people needed to vaccinate to achieve a certain health outcome.
- How do we define the desired outcome given the policy question? Selecting a desired modelled outcome to evaluate depends on the underlying policy question. For example, for a policy question related to reducing disease and health burden, the number of deaths, cases or

hospitalizations averted, disability-adjusted life-years (DALYs), or quality-adjusted life-years may be considered. For a policy question related to ensuring adequate health-care capacity, it may be helpful to evaluate the number of hospitalizations averted, the probability of an outbreak, or the probability of service disruptions. Additional outcomes of interest may include the number needed to vaccinate to avert a case of cervical cancer or an incremental cost–effectiveness ratio. It may be possible that the policy question requires evaluating multiple outcomes.

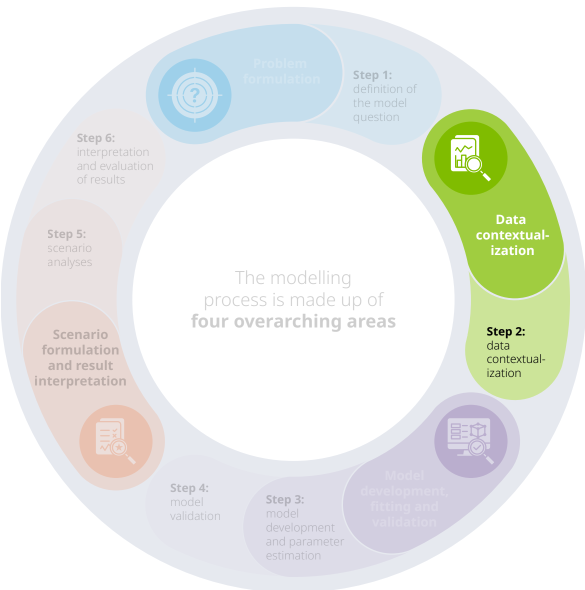
HPV vaccination example

For a model of HPV vaccine introduction that aims to explore the impact of different targeted age groups and a single-dose versus a two-dose schedule, the following assumptions and scenarios could be made:

- Different scenarios of vaccine introduction, including different targeted age groups (age 9–10 years versus age 11–12 years) and different dosing strategies (one dose versus two doses), and additionally no-vaccine scenarios to estimate impact.
- Vaccine effectiveness for one dose versus two doses, such as against persistent HPV infection of HPV types included in the vaccine, against precancerous lesions, or cervical cancer incidence.
- Health outcomes, such as number of cervical cancer deaths averted.
- Vaccination coverage levels for one dose versus two doses and age groups (e.g. among people aged 9–12 years).

Consider how we can translate the policy question “What will be the health impact of introduction of an HPV vaccine among specific targeted age groups and with one dose versus two doses?” to modelling questions and the outcomes we may want to consider:

- Is the number of estimated deaths averted lower in scenarios with implemented school-based immunization programmes?
- How do variations in vaccination coverage affect the incremental cost–effectiveness ratio?



4.2.2 Step 2: data contextualization

Next comes gathering and understanding the data and epidemiological landscape, including the underlying biology. This step involves identifying what information is available, recognizing gaps or limitations, and finding alternative solutions, such as using data from similar settings.

Key questions for consideration

- What data were used? Are they representative of the population of interest?
- Where did the data come from?
- How were data gaps addressed?
- Was a quality assessment conducted?

Models are only as good as the data they rely on.

Models are only as good as the data they rely on. After defining a question for the modelling exercise, the next step is to create a list of data necessary to answer the question of interest. These data may include information on vaccine coverage, historic cases and outbreaks, the immunity or susceptibility profile within a population, and other demographic considerations. These data come primarily from national databases, but they may also be reported in the WHO Immunization Dashboard *(22)* and disease surveillance databases.

Data sources commonly used in modelling

The following list of data sources commonly used in modelling is not exhaustive and may be more or less appropriate, depending on the specific modelling question under consideration:

- **Case notifications**: most vaccine-preventable diseases (e.g. diphtheria, measles) are notifiable in many settings. Public health agencies and ministries of health typically maintain records of reported cases by age, location and date. These data can inform models, but they are often biased due to underreporting and lack of laboratory confirmation – particularly in low-resource settings with endemic transmission. Key additional considerations include case definitions, reporting systems, test positivity rates, and laboratory confirmation using immunoglobulin M antibodies or polymerase chain reaction.
- **Outbreak reports**: reports from outbreak settings may provide information on the number of cases or deaths or the case fatality ratio, and other key risk factor information such as vaccination status and age.
- **Vaccination coverage**: for the disease of interest, a vaccine may already be implemented in the immunization programme. Alternatively, a vaccine under consideration may be planned to be delivered at an already existing immunization touchpoint. In either case, it is important to collect information on vaccination coverage for relevant vaccine doses in the population of interest.
- **Demographic data**: models often require information on birth rates, population structure and age-specific contact patterns. These may come from vital registration systems, census data, or studies from collecting contact diaries. Death registries, including vital registration systems, sometimes include information on cause-specific mortality, but they may not capture the entire population of interest, especially mortality among young children (e.g. measles-specific mortality is infrequently captured accurately).
- **Serological data**: serological data may be helpful to inform the susceptibility profile across age, space or time in the setting of interest. It may also help to inform estimates of vaccine effectiveness and potential waning of vaccine-induced protection. These data, however, may be only infrequently available and reported and may be limited to specific subpopulations, reducing the generalizability of the data across broader settings or time periods.
- **Scientific publications**: searching the literature for scientific studies or modelling studies in other settings may be a useful step in data-gathering. Some model parameters, such as specific disease characteristics, may be informed by data from other settings.

It is imperative that the data are appropriate for the population of interest. This includes being from the specific study setting (e.g. a model in Country X should include as much data as possible from Country X), from the population of interest (e.g. among children aged under five years, or among internally displaced people), and from a comparable epidemiologic setting (e.g. from real world setting instead of clinical trial, if available) or time period (e.g. prioritizing using data generated in the last few years over data generated decades previously). Ideally, local data should be used as input to the model. If a specific data source or type is not available and it is not feasible or worthwhile to collect it for either the location or population of interest, an alternative source may be considered, providing it is still relevant and applicable to the specific context. It may be necessary to discuss this with the study team (e.g. the NITAG or RITAG working group) to determine the appropriateness and acceptability of any necessary modifications and assumptions.

Frameworks such as health technology assessments include existing approaches, systems and tools for assessing geographical transferability (using information from one country or region in another country or region) *(23)*. Decision-makers could use these tools to assess transferability based on input data and to make decisions about using and adapting models. This is also an opportunity to advocate for improved data collection or quality, if appropriate.

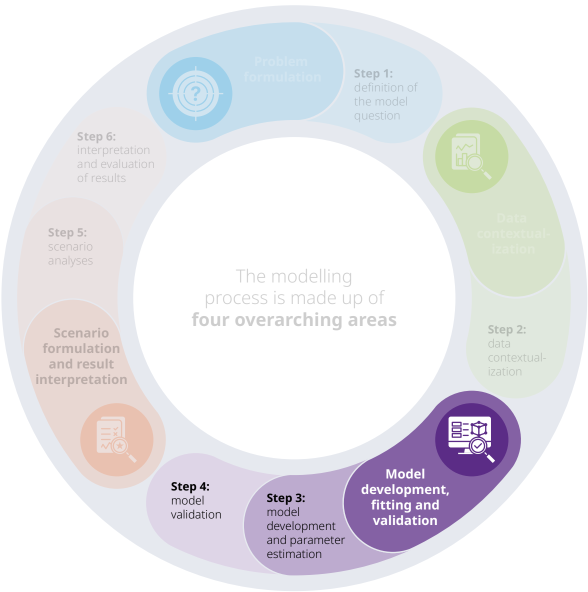
Note that global models may require different data sources, and local data and context may not be necessary. In the case of global models, the WHO Global Health Observatory could be a resource to provide standardized input data across countries *(24)*.

4.2.3 Step 3: model development and parameter estimation

With the data as the foundation, model development can begin. This involves choosing the right structure or specification (e.g. which age groups are included) for the model and designing the software or code that will allow the model to be implemented. When modellers refer to a "model", they often mean a set of equations that represent how a system behaves, which are then translated into computer code to be evaluated efficiently using appropriate software programs. *See Annex 2* for more information.

Once the model is built, the difference between the model's predictions and the observed data is assessed. Differences are usually found; if so, the differences are reduced to approximate the observed data as close as possible. This process is called parameter estimation. *See Annex 2* for more information.

Understanding the impact and limitations that simplifying assumptions may have on the model results is important. Additionally, it is important to understand the multiple sources of uncertainty contributing to the model results. *See Annex 3* for further details.



4.2.4 Step 4: model validation

Model validation involves comparing the model outputs with real-world data or expected patterns to make sure the model is producing credible results. This helps ensure the model is suitable for supporting decisions. *See Annex 4* for further details.

Girls in Uzbekistan following vaccination against HPV
© WHO

4.2.5 Step 5: scenario analyses

Scenario analyses allow examination of various possibilities to see how different versions of the future might evolve, such as the effects of implementing a different vaccination strategy. *See Annex 5* for further details.

4.2.6 Step 6: interpretation and evaluation of results

Interpretation and evaluation of results are the last critical steps. Comparing different scenarios with a baseline (status quo) helps to clarify the impact of potential decisions. Communicating the model and its results should involve clear and plain language, information about model assumptions and uncertainty, and the limitations of the model. Where possible, visual formats can help people to process information. This helps policy-makers and other stakeholders to understand the findings and better judge their potential validity. *See Section 5* for further details.

Empirical validation of the model predictions is the final evaluative step of the modelling process. This validation may need to occur years after the modelling results are finalized. Knowing in retrospect how models performed, where they failed, and what assumptions were correct or incorrect are crucial to the modelling scientific endeavour.

5. How should modelling results be interpreted and evaluated?

Key messages

- When evaluating a model and its results, the following key areas should be assessed:
  - What is the main outcome of interest?
  - If the outcome is a composite of other metrics, what are the main outcomes contributing to the composite outcome?
  - For these key outcomes, are the main pieces of evidence included, such as direct and indirect effects, burden of disease, vaccine effectiveness and duration of protection?
  - Is uncertainty in these key outcomes explored sufficiently?
  - Do the outcomes change qualitatively within the explored uncertainty?
  - Do model results intuitively make sense?
- There is never a single "correct" model for all questions, and different models make different assumptions. Assess whether the modelled outcomes answer the specific policy questions.
- Recognize that all models have limitations, and their outcomes are inherently estimations. Model outputs have varying degrees of uncertainty and thus may capture future realities inaccurately, but it is important to assess whether it is qualitatively informative.

Mathematical models provide valuable insights into assessing the potential impact of health interventions, but they are only one piece of the broader evidence base. To interpret model results effectively, decision-makers must interpret the results in the context of model assumptions, local context, operational realities or constraints, and other reliable data sources. In addition, interpreting model results is an iterative process that evolves with updated data and changing circumstances. This section outlines a structured approach to understanding the applicability of model outcomes to the local context (e.g. cultural and logistical factors), highlights critical questions to ask, and provides practical examples to contextualize results.

Key questions for consideration

- What can be learned about the policy question from interpreting modelled outcomes and scenarios?
- What are the most important model findings? How might they provide insights for the decision?
- For what period of time were impacts measured?
- What assumptions were tested across a range of scenarios?
- Is the full range of uncertainty around key parameters explored sufficiently?
- Do key model results change qualitatively within the observed range of uncertainty of key parameters?

Once the model results have been obtained, the next stages are to interpret the results and then share the results and conclusions with stakeholders and the general public.

5.1 Evaluating the relevance of the model

Understanding the purpose of the model – commissioned either by the policy-maker or independently by a modelling team – helps to assess whether the results are relevant to the policy question.

HPV vaccination example

For the question "What will be the health impact of introduction of an HPV vaccine among specific targeted age groups and with one dose versus two doses?", the NITAG has identified a model in the literature that estimates the number of cervical cancer deaths averted from introduction of an HPV vaccine.

To ensure the model is relevant, sufficiently detailed and related to the question, by framing the model in the context of the specific policy question, the following questions could be asked:

- What policy question or intervention does the model aim to address?
- How relevant is the model to the specific context (e.g. demographics, health systems)?

The identified model explores scenarios of HPV vaccine introduction at health facilities among girls aged 9–12 years and estimates subsequent cervical cancer incidence and number of deaths averted. Scenarios include coverage at different levels and among various age ranges targeted for vaccination delivery. This model is implemented using data from a neighbouring country with similar demography.

Exploring the impact of different HPV coverage levels on the number of deaths averted and the target age of vaccination are both relevant to the policy question.

The scenarios explored and the underlying demography are relevant to the setting, but it is important to note this model considers vaccination only of girls, which is different from the policy question and the results should be interpreted in light of this difference.

5.2 What key questions should be evaluated?

Evaluating models is an iterative process. To review the results of a model, start by considering the desired outcome of interest (e.g. cases of cervical cancer averted) and then ask the following questions:

- What are the key drivers and assumptions that inform the outcome of interest?
- Do these sufficiently incorporate existing data, local relevance and uncertainty?

This process continues until there is either a fatal flaw or confidence that the model has captured the key drivers of the policy outcome of interest. These considerations are outlined in Steps 1–3 below. Following a satisfactory evaluation, proceed to Step 4 to interpret outcomes and scenarios.

5.2.1 Step 1: what methodology did the model use, and what assumptions did the model make?

Understanding how the model works, and the assumptions it makes, is critical for evaluating the relevance and usefulness of the model. Start with the most important model outcome for the question of interest.

We want to interrogate how the model works and what assumptions were made to run the model and produce this outcome of interest (e.g. cases of cervical cancer). Some specific questions to ask include:

- What type of model is used (e.g. compartmental, agent-based), and how is it capturing specific mechanisms of interest (e.g. transmission, contact rates)?
- What assumptions does the model make about disease dynamics and progression (including deaths)? These assumptions include important aspects of the epidemiology of the pathogen, such as severity of illness, how the pathogen is transmitted between individuals or groups, characteristics of this transmission (including herd protection) and characteristics of immunity (e.g. waning).
- What assumptions does the model make about the interventions, such as vaccine introduction, duration of vaccine-induced protection, vaccine-induced protection against infection, infectiousness, symptomatic illness, complications and deaths?
- What assumptions does the model make about behaviours, such as number of contacts by age group?

It is important to consider how these assumptions were chosen, and how realistic they may be. Modellers may have conducted sensitivity analyses to explore how changes in key assumptions may impact the model's outcomes. Most critically, it is important to evaluate whether the model correctly incorporates key mechanisms (e.g. the effect of the vaccine). This includes how different intervention scenarios are constructed, assumptions on vaccine efficacy, and whether the vaccine protects against infection, disease or transmission. Implementation of these mechanisms and assumptions in the model should be in agreement with data and evidence from existing clinical trials and other post-licensure studies, if available.

While reviewing the model, write down key assumptions and any discrepancies between these and prior understanding, identify any unsuitable assumptions, and consult experts to determine their influence in the modelled outcomes. If there is a possibility for follow-up work or additional modelling, *see Section 3* for more details on working together with modelling teams.

HPV vaccination example

HPV vaccines prevent infection with vaccine-type HPV serotypes, which can progress into cervical lesions and develop into cancer. We are interested in evaluating how the model tracks this process, and how people develop cervical cancer, considering the target population, health system and demography.

We may not know how modelling assumptions were chosen, so we can only assess how realistic they are given our expert knowledge and specific setting context. If possible, discuss how any assumptions were chosen and implemented with the modelling team.

The following key areas should be evaluated:

- What type of model (e.g. compartmental, agent-based) was used, and is it appropriate?
- Which HPV serotypes are included in the vaccine versus those included in the model?
- What are the risks of HPV infection, lesions and cancer by serotype?
- What is the vaccine efficacy by serotype, including cross-protection? Is the model built such that the vaccine prevents infection rather than transmission?
- What is the probability of sexual interaction between age groups and sexual behaviour?
- How long is the time window to accumulate impact?
- Are there any biological or behavioural considerations (e.g. vaccine efficacy, serotype prevalence, sexual behaviour) that differ between girls and boys?

5.2.2 Step 2: what is the quality of the data used, and its relevance to the setting?

Models rely on data to ground their predictions in reality. Decision-makers must critically assess the quality and applicability of the inputs used to fit the model. *Revisit Section 4.1.2* and then ask the following questions:

- What data were used, and are they representative of my country or region? Possible data included in models encompass vaccine efficacy or effectiveness, age-specific incidence, case fatality, vaccination coverage and timeliness, and demographic characteristics (e.g. population size by age, estimated live births).
- Where did the data come from? Data may be from observations from trials or other empirical studies, or from estimates from literature reviews or other modelling projects.
- Are the epidemiological setting and time period of the empirical studies relevant to the policy question? Consider any related implications regarding uncertainty and appropriateness.
- Were there any significant gaps in the data, and how were they addressed? This could include the absence of information or missingness. If so, were additional assumptions made, were data extrapolated from other sources, or was information borrowed from other settings? It is important to evaluate whether a quality assessment of the data (e.g. using the GRADE framework) was made.

HPV vaccination example

Since the outcome of interest in the HPV vaccination example is the number of cases of cervical cancer, we assess the source of incidence data by asking the following questions:

- What reporting system was used to capture cases?
- What definition of cervical cancer cases was used?
- If there were no reliable local or national data on cervical cancer cases, what alternative data (e.g. case fatality ratios) were used or assumptions made?
- What assumptions were made for screening and treatment options and capacity in the country? How well do they influence the outcome of interest over long time horizons?

The data available captured the number of cervical cancer deaths and case fatality ratios. Therefore, the model needs to compute backwards to find the incidence of HPV. The case fatality ratio was assumed from results of a systematic review and meta-analysis of cervical cancer case fatality ratio by serotype. The number of deaths was captured from a cancer registry database. No quality assessment of the death data was performed, and so decision-makers may need to proceed with caution.

5.2.3 Step 3: what does the output uncertainty represent, and what insight does it provide?

All models have uncertainty. Decision-makers must understand the sources and implications of the uncertainty to make informed decisions. When reviewing a model, consider the following:

- What are the main sources of uncertainty in the model? Consider the following:
  - What was the model structure, and how did the model fit to the data? Was the model stochastic or deterministic, and what was not included in the model for simplicity?
  - Was uncertainty in data sources included? If so, how?
  - Were ranges of input parameters tested, including from epidemiological, health system, vaccine and operational considerations?
  - What assumptions were tested across a range of scenarios?
  - Across what period of time were impacts measured? Including more time in the future will increase the range of uncertainty.
  - What population was modelled? Interpreting estimates over a country's entire population should yield higher uncertainty than over a subset or smaller community.
  - Are there any concerns related to dose dependencies in the model structure? This is called tracing and refers to tracking how many people have received how many vaccine doses over time.
  - What additional assumptions were implemented that may impact what uncertainty from the real world was or was not captured? For example, instantaneous applications (i.e. all at one moment in time) of vaccine campaigns or supplemental immunization activities, which is unrealistic, may lead to less uncertainty in the model but may not fully capture real-world variability (i.e. doses are realistically delivered over weeks or months, and perhaps in stages by geographical location).
- How sensitive are the results to changes in key parameters? This may be tested via sensitivity analyses of parameters (i.e. an exploration of plausible bounds).
- How will uncertainty affect the decision? It is important to assess whether the decision will differ

significantly based on where it sits within the uncertainty range. For example, a range of incremental cost–effectiveness ratios given a country-specific threshold may lead to different conclusions.

HPV vaccination example

We have a deterministic model with no uncertainty included from data sources. The only uncertainty captured in the model outputs are from the model fitting process. This suggests that not much of the uncertainty in the process was captured, and the results should likely be interpreted cautiously.

A sensitivity analysis was conducted to test whether different estimates of vaccine effectiveness (within a reasonably plausible range) changed the overall prioritization across different scenarios. Another sensitivity analysis was conducted to assess whether adjusting the rate at which cervical lesions develop into cervical cancer among vaccinated people changed the overall output across different modelled scenarios. In both sensitivity analyses, relative rankings of scenarios by the number of cases averted did not change. Therefore, we can be more confident in the model than if these rankings had changed.

Indonesia: Immunization Heroes, September 2024
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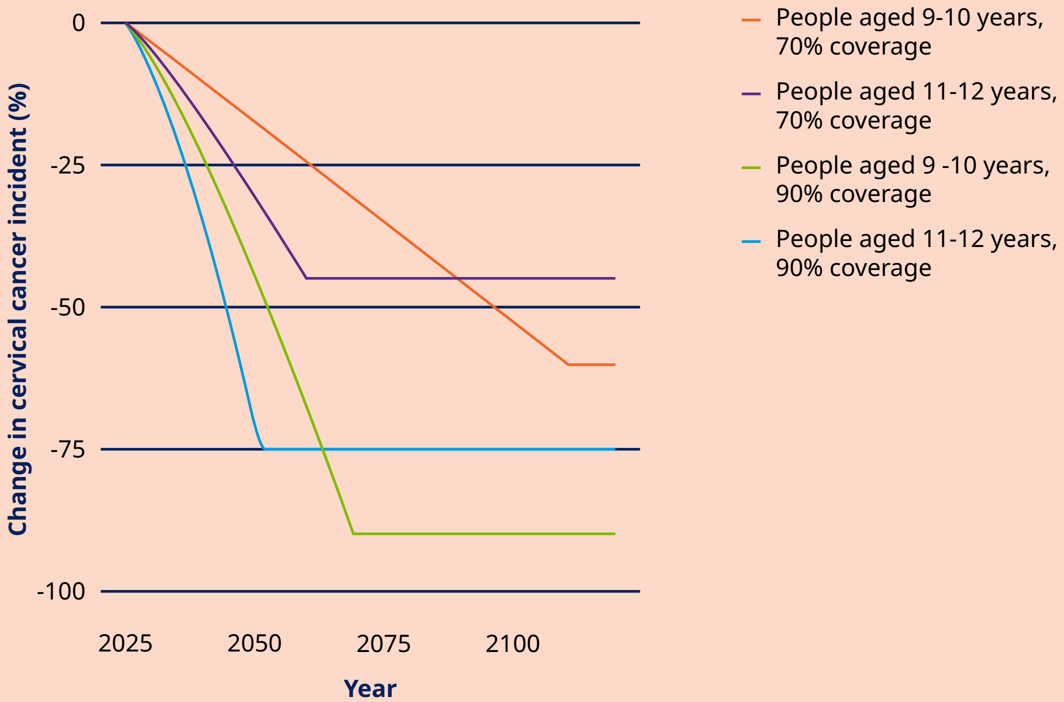
Common mistakes in interpreting model results

When comparing model results across scenarios, it is important to consider the time period over which the results should be evaluated. For example, as shown in *Figure 5*, different conclusions may be drawn on the optimal target age if considering health impact over a 25-year period (targeting people aged 11–12 years) instead of a 100-year period (targeting people aged 9–10 years).

Fig. 5. Example model results of HPV vaccination scenarios



5.2.4 Step 4: what can be learned about the policy question by interpreting outcomes and scenarios?

After considering model mechanisms, assumptions, data and uncertainty, the model results are evaluated in the context of the broader decision-making process. Considerations include whether the model incorporates specific contextual factors or other important cultural practices that might influence human behaviours (e.g. vaccination rates).

Now we can see what the model is demonstrating and contextualize it relative to other factors, including data and uncertainties. Some important questions to consider are:

- What are the most important findings, and how might they provide insights for the decision to be made?
- How do the modelled scenarios compare with the status quo? Are there any alternative strategies or scenarios that improve the outcome of interest?
- How well does the model fit the data, and does it make epidemiological sense?
- What is the model uncertainty demonstrating about the model output relative to the decision

in the specific context? Are uncertainty or confidence intervals across scenarios overlapping (suggesting one scenario may not be superior to another), or are they not overlapping (suggesting a superior scenario)?

How do we know whether the model fits well to the data and makes epidemiological sense?

It is possible to evaluate how well a model fits quantitatively via investigations of the model fit. Quantitative metrics to assess this include mean error and mean absolute error.

The model fit should also be evaluated qualitatively. This requires checking that the model output can closely replicate the data used in model fitting for calibration to historic years (i.e. the "known" truth before time periods of scenario analyses – the unknown future).

Although this is a crucial step, a good fit to historic data does not necessarily mean a model is suited well for scenario analyses. Models may be "overparameterized" by having more parameters than necessary to fit the data. An overparameterized model may fit to historic data too well – including picking up any deviation and noise – and generalize to future scenarios and predictions poorly.

Additionally, it is important to consider whether the data being fit to are incomplete and how this may affect the model outcomes. Check the fit parameter values make epidemiological sense. Look for implausible trends or outcomes, such as predictions that deviate significantly from observed data without clear explanations. When results are counterintuitive, consult modellers or disease experts to understand whether the discrepancy arises from valid insights or errors.

It is possible to evaluate how well a model fits quantitatively via investigations of the likelihood of the model fit. The likelihood or log-likelihood is a quantitative metric of the probability that the model results will occur given the data the model was calibrated against.

5.3 What is next?

One of two conclusions may be reached following review of the model: either there are substantial concerns that preclude moving forward, or we are interested in translating these results into action.

HPV vaccination example

We identified an HPV model published in the literature for a similar demographic and epidemiological setting to our country. The model evaluates outputs that are similar to our policy question – what would be the health and economic impact of an HPV vaccination introduction among children aged 9–10 years and children aged 11–12 years, and using one dose versus two doses in our country?

The model uses an appropriate model structure. It is deterministic and does not include uncertainty from input data sources. It fits to cervical cancer incidence data. It assumes vaccination only among girls, which is different from our interest in vaccination among girls and boys. It tests sensitivity analyses of vaccine effectiveness and rates of cervical cancer development from cervical lesions among vaccinated people. We are in agreement about assumptions that the model makes about contact patterns, sexual behaviour, serotype-specific transmission, and serotype-specific vaccine effectiveness. The model estimates the number of cervical cases averted over the next 100 years.

The following scenarios were tested and compared with a status quo (i.e. no vaccine introduction) scenario. All scenarios confidently estimate an increase in the number of cases averted (i.e. a reduction in the number of cases). The confidence interval for the scenario with introduction among children aged 9–10 years with one dose reaching 80% coverage does not overlap with the confidence interval for any other scenario after 100 years. Therefore, we can be mildly confident that if the country can introduce an HPV vaccine among children aged 9–10 years that reaches 90% coverage, we may maximize vaccine impact and minimize future health burden. We will discuss this with implementers in the country to discuss feasibility of the introduction.

At a later date, subsequent evidence on immunological longevity and empirically observed reductions in clinical outcomes will likely be made available. At that time, retrospectively validating original model-based policy will be critical.

It is important that models are communicated responsibly for transparency and reproducibility. This helps gain the trust of stakeholders and the broader modelling community. Transparent reporting includes clearly communicating and documenting which data sources were used as inputs; which outputs were measured; which model structure was used; any simplifying assumptions that were made; the software or computer code that was implemented; estimated and assumed parameters; which validation was performed; which scenarios were considered; the uncertainty of the results; and any limitations.

Depending on the study design of the particular modelling question, checklists can assist in ensuring responsible communication and publication, such as:

- Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) (https://www.equator-network.org/reporting-guidelines/gather-statement/) for global health estimates.
- Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (https://www.equator-network.org/wp-content/uploads/2013/04/Revised-CHEERS-Checklist-Oct13.pdf) for economic evaluations.
- EPIFORGE (https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003793), for epidemic forecasting and prediction

Key considerations for interpreting modelling results include generalizability and feasibility. The generalizability of the available insights may vary across studies and settings, and according to the nature of the insights. This may limit the ability to apply the modelling results to the local setting. Generalizability refers to how well the results of one modelling study are applicable to another setting. Generalizability requires information on what parameters, values and ranges were used in the model, how the vaccine intervention was modelled, and differences in populations and pathogen epidemiology between locations. Regardless of whether the available models were developed for global, regional or local contexts, there may still be some applicability to a specific location. Consider the following factors that could affect the generalizability of modelling results:

- What are the vaccine characteristics (e.g. efficacy, duration of protection, dosing schedules, delivery methods), and how would these impact effectiveness in the setting? These generally do not vary much across populations, unless the pathogens vary between locations (e.g. in genotype).
- What is the population demography, health-seeking pattern, transmission dynamics and pathogen epidemiology, and how might these impact vaccine interventions? These are more likely to vary in different contexts.
- What health-care infrastructure is in place (e.g. service delivery capacity, vaccine supply chains, cold-chain storage), and how would these impact coverage and effectiveness of vaccine programmes?
- What are the characteristics of the population (e.g. income, education), and are there disparities that might influence vaccine access, acceptance and utilization?

As an example, consider the factors that may strongly influence results for the following vaccination programmes or diseases:

Disease example 1: chikungunya

Different delivery platforms have different costs. It is important to consider how delivery costs may impact the cost-effectiveness of the intervention. For example, a reactive chikungunya immunization campaign may have higher costs than delivery via an existing routine immunization programme. Other factors that may influence the cost-effectiveness of an intervention include subnational campaign tailoring, vaccine price and assumed disease burden metrics (e.g. DALYs).

Disease example 2: hepatitis A

Demographics and pathogen epidemiology may change across study locations and may differ between data where the results were generated from and the local setting. For example, the burden of hepatitis A may be concentrated in children in a published modelling study, but concentrated in adults in the setting of interest in the model. Considering introduction of hepatitis A vaccination into routine childhood immunization programmes, therefore, may be less applicable than considering a life-course approach.

Disease example 3: influenza

Some diseases and their vaccines have additional complications to consider, such as which age groups are being infected, lower vaccine effectiveness, and the need for booster immunizations. For example, influenza traditionally infects people of all ages, but the oldest and youngest people in a population tend to have most severe disease. Influenza vaccination has relatively low effectiveness, and the immunity provided does not last from year to year due to waning antibodies and changes to circulating virus strains. These considerations may need to be incorporated into a model to understand dynamics in a population and may not be generalizable across settings.

Disease example 4: dengue

As new vaccinations are surveilled following licensure, rare outcomes not significantly observed in clinical trials may be identified. Any potential new risks may have implications on the perceived value and benefit of introduction and influence translation of former modelling results that may not account for these phenomena. For example, post-licensure surveillance of a dengue vaccine revealed safety concerns related to antibody-dependent enhancement. A new vaccination product has since come to market, but this process required new modelling incorporating updated knowledge on the safety and new vaccine characteristics.

Disease example 5: HPV

When modelling the impact of the HPV vaccine, some findings can be generalized, such as the vaccine's effectiveness in preventing HPV infections and reducing cases of cervical cancer. These effects are well documented and expected across different populations with similar vaccination rates and health-care access. The exact magnitude of impact will vary, however, based on factors such as baseline HPV prevalence, vaccine uptake, health-care infrastructure and behavioural differences. Additional assumptions about susceptibility, serotype specific prevalence and screening programmes may affect generalizability across broad settings.

Deviations become concerning when real-world data differ significantly from model projections, such as lower-than-expected reductions in HPV cases or mismatches in assumed versus achieved vaccine coverage. Models built for high-income settings may not apply to low-resource areas with weaker health-care systems. Key warning signs that the model was not generalizable include large gaps between predictions and observed outcomes, highlighting the need for ongoing model validation and adjustments to ensure realistic estimates of vaccine impact.

After determining whether model estimates are generalizable or applicable to the setting, several criteria beyond the disease burden, vaccine impact and cost-effectiveness must be considered. A main consideration should be whether the scenarios or intervention are feasible to implement and execute. Feasibility encompasses not only whether the setting can or cannot do something, but also what steps or actions may be needed to accomplish the objective or intervention, such as vaccine introduction. Feasibility considerations include:

- whether a vaccine can be incorporated into an already existing EPI schedule, rather than having to establish a new platform (e.g. an adult immunization touchpoint);
- how long it may take to plan and implement a successful vaccine campaign;
- whether an affordable financing option is available;
- whether there is public interest and buy-in to an additional vaccination, change in delivery schedule and/or booster dose.

Additionally, it is critical to consider whether an intervention is equitable *(8)*. This is usually part of consideration for broader decision-making process (e.g. criteria for the evidence-to-decision framework). Equity considerations include:

- whether vaccination services are accessible to the entire target population, including people from vulnerable and hard-to-reach populations;
- whether vaccination generates non-health-related effects;
- whether there is stigma around the disease, vaccination, or alternative preventive or control measures.

Some of these equity-related considerations could be assessed quantitatively through transmission models and economic evaluations *(25)*, provided there are data of sufficient quality and quantity with equity dimensions, such as subgroup-level data on susceptibility to infection, disease risk, care-seeking, and opportunity cost of health-care interventions.

Despite model estimates suggesting favourable outcomes, implementation of vaccine introduction or other interventions may not be feasible or possible. Additional modelling may be considered to explore scenarios with more feasible implementation specifications for the setting.

5.4 Evaluation of the modelling and translation process

Defining "success" in modelling is an important step that should be established at the outset of the modelling process *(26)*. Success in modelling can be understood through multiple dimensions, including the following:

- Valorization success refers to the model's utility and relevance to its intended audience and objective. The appropriateness for purpose is demonstrated by its influence on policy decisions.
- Predictive validity or success evaluates whether observed outcomes (e.g. disease incidence) fall within the model uncertainty range, indicating robustness and reliability.
- Procedural success assesses whether the model was developed in accordance with best practice guidelines in the field, ensuring methodological rigour and transparency.

It is critical to evaluate the translation process itself (e.g. how well communication was facilitated) and the outcome of translation (including both direct and indirect implications) after the project concludes. Translating model results could result directly in policy recommendations. Additionally, modelling results may indirectly impact policy- and decision-making by identifying gaps in data or other types of evidence. Understanding how the model and its translated results have shaped decision-making is imperative for improving future models and projects to inform future decision-making.

Translated model results should be evaluated on different timescales following the immediate project period, including in the short term (e.g. to determine whether it has been translated adequately, to review how or what policy options were formed) and in the long term (e.g. for re-examination as new evidence becomes available). Results of model translation should be communicated to modellers. *See Section 3* for best practices on how to facilitate this communication.

An example of a way to evaluate the translation process could include a workshop with modellers and model users. The objectives could be to work through the policy recommendations and relate back to the model, data and operational strengths and weaknesses. Workshop attendees could discuss key points of uncertainty and move from the model results to actionable recommendations.

5.5 Conclusion

Mathematical models are powerful tools that use data to provide actionable insights and evidence that can be used by decision-makers to compare strategies and anticipate outcomes such as disease burden and cost-effectiveness of vaccination programmes and interventions. When grounded in the local context and developed through transparent, multidisciplinary collaborations, models can guide immunization policy even in data-limited settings. By embracing the iterative nature of modelling and coupling it with local expertise, stakeholders can better design and deliver vaccination programmes that save lives and optimize health impact.

Malawi: HPV awareness and vaccination for cervical cancer prevention, July 2024
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Annex 1

Modelling project phases, tasks and team member responsibilities

Project phases	Task	Decision-makers	Modellers	Advisory bodies	Public health officials	Disease specialists	Vaccine manufacturers	Implementers	General public
Problem formulation	Advise on priorities for research and modelling								
	Define decision problems								
	Translate policy question into quantifiable modelling questions								
	Advise on feasibility assessment								
	Synthesize knowledge on disease and vaccine/clinical trials								

Project phases	Task	Decision-makers	Modellers	Advisory bodies	Public health officials	Disease specialists	Vaccine manufacturers	Implementers	General public
Data contextualization	Conduct an extensive literature review to understand the broader views of similar questions and existing modelling work on the topic in various settings								
	Review model structures, assumptions and parameters								
	Review roles and dose regimens of vaccines in the model								
	Review the assumptions about the disease and transmission								
	Assess the feasibility of vaccine implementation								
Model development, fitting and validation	Ensure data are parameterized correctly for the model								
	Help identify the sources of data for modelling								
	Review data inputs and data for model validation								
	Review or provide data related to vaccine characteristics and efficacy								
	Review or provide data related to disease characteristics								

Project phases	Task	Decision-makers	Modellers	Advisory bodies	Public health officials	Disease specialists	Vaccine manufacturers	Implementers	General public
Scenario formulation and result interpretation	Perform scenario analyses and sensitivity analyses								
	Review scenario formulation and interpretation								
	Assemble model results								
	Provide feedback on practical points regarding the model scenarios								
	Review vaccine scenario construction and interpretation								

Darker shading indicates a main role and lighter shading a minor role for members of different project tasks.

Annex 2

Model development

Key questions for consideration

- What type of model will be most appropriate to answer the policy question of interest?
- How will the model be assessed to determine whether it fits to the data and whether it makes epidemiological sense?
- What outcome measure should the model estimate to best answer the policy question of interest?
- What model structure will best capture the main sources of uncertainty?
- How will the model incorporate key mechanisms of disease epidemiology, dynamics and progression, transmission patterns, population behaviour, immunity and vaccine introduction?
- How will model assumptions be made to align with available data and evidence? On what basis will these assumptions be made? How realistic will they be?
- How will these key assumptions and mechanisms in model structure impact model results?
- How will the number of vaccine doses received (dose dependencies) be tracked in the model structure?

With an understanding of the question of interest and the data available, model development can begin. The first step in model development is selecting an appropriate model type. There are many different types of mechanistic model that modelling teams may choose to implement. The most common are compartmental transmission models and network models.

Compartmental transmission models group the population into categories, or compartments, based on relevant characteristics such as infection history or immune status and accounts for key features of disease progression. A SIR model – in which the population is divided into people who are susceptible (S), infected (I), or removed or recovered (R), and people in the population move between these different states – is an example of a compartmental transmission model.

In network models, networks of individuals interact in a contained system, which accounts for more details of the disease spread – such as specific patterns of behaviour – which may be important to capture for understanding disease transmission. An agent-based model is an example of a network model.

Depending on the type of question being asked, some model types may be more appropriate than others.

Following model development, a corresponding economic evaluation model, such as a cost–effectiveness model – which estimates the predicted cost of interventions and compare costs with estimates of health burden – may be built, depending on the policy question.

These types of model can take output from infectious disease models, such as disability-adjusted life-years (DALYs) or number of deaths averted, along with information on product and delivery costs, including costs to communities, to generate estimates of key economic indicators. These include cost–benefit ratios and incremental cost–effectiveness ratios, which can be instrumental in generating policy decisions. There are many additional resources on these types of modelling extension *(1)*.

Some models use spreadsheets such as Excel workbooks. Other models use software such as Python, R or proprietary systems. Regardless of how the model is developed, simplifying assumptions must be made to ensure it is feasible to construct the model. For example, modellers may choose to consider a population that includes births (an "open population") or does not include births (a "closed population"). Depending on the research question and the time horizon, this may have significant impacts on the model results. It is important to communicate with the modelling team to understand which assumptions are being made, to discuss the acceptability of the assumptions, and to evaluate which assumptions may critically compromise the integrity of the model.

In addition to discussing simplifying assumptions, it is critical to have ongoing conversations with the modelling team. Model development is an iterative process that requires collaboration and communication with the project team to ensure key understanding of disease processes, assumptions and how outcomes are captured.

Parameter estimation

We do not always have all the information on each parameter. Models often need to estimate key parameters with unknown values by fitting or calibrating models to data – making an inference. There are multiple ways models can be fit to data using different statistical techniques, including deterministic optimization such as maximum likelihood estimation and Bayesian methods such as Markov chain Monte Carlo simulations.

Instead of estimating a parameter, some modelling teams take their prior knowledge and the available literature to make a best guess at what a parameter may be, and then use that value instead of estimating the value in the model. This may depend on how many other parameters need to be estimated and the quality of evidence available for each parameter before the modelling study starts.

Many resources and courses on model inference are available, including:

- Funk S, Camacho A, Johnson H, Minter A, O'Reilly K, Davies N. Model fitting and inference for infectious disease dynamics. London: London School of Hygiene & Tropical Medicine; 2024 (https://sbfnk.github.io/mfiidd/).
- Wesolowski A, Hill A, Gurley E, Truelove S. Infectious disease modeling in practice. Johns Hopkins University, Baltimore, MD; 2024 (https://www.coursera.org/learn/infectious-disease-modeling-in-practice).

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Annex 3

Understanding and addressing uncertainty in models

All mathematical models include some level of uncertainty because they simplify complex real-world systems. This uncertainty arises from several sources:

- **Structural uncertainty** arises from assumptions made about how a disease spreads or progresses, reflecting gaps in scientific knowledge.
- **Parameter uncertainty** comes from not knowing the exact values of key inputs, such as vaccine efficacy or transmission rates.
- **Heterogeneity** introduces uncertainty when individual differences, such as age or health status, are averaged within the model.
- **Stochastic uncertainty** captures random variation between individuals that cannot be explained by their characteristics or reduced by using more data.

Recognizing these different types of uncertainty helps decision-makers interpret model results with appropriate caution.

Even when two studies provide the same estimates, it is important to be critical of the studies and look at their inherent uncertainties, regardless of them being in agreement. This is because the studies may capture different underlying uncertainties in their modelling processes. For example, parameter uncertainty reflects the uncertainty in estimating outcomes, such as whether a disease will become severe or stay mild, which can depend on factors such as sample size or the data sources used in the model. On the other hand, stochastic uncertainty accounts for both population-level uncertainty and variations in individual experiences, where people in the same situation may have different outcomes (e.g. one person might recover from measles in a week, but another person may take two weeks to recover). A model that does not include stochastic uncertainty is called a deterministic model.

Visualizing uncertainty

Communicating uncertainty in model outputs to all audiences is important *(1–3)*. Model results often include a range to show uncertainty around a point estimate, which is the most likely outcome. The size of the range depends on the level of confidence in the model itself and its predictions. A wider range indicates greater uncertainty, while a narrower range suggests more confidence in the estimate. For example:

- A model might estimate 300 000 cases of dengue over 10 years, with a range from 250 000 to 375 000 cases.

- Another model might estimate 300 000 cases of dengue over the same time period, with a range from 200 000 to 425 000 cases. This has a wider uncertainty range and, thus, less confidence.

Confidence versus uncertainty intervals

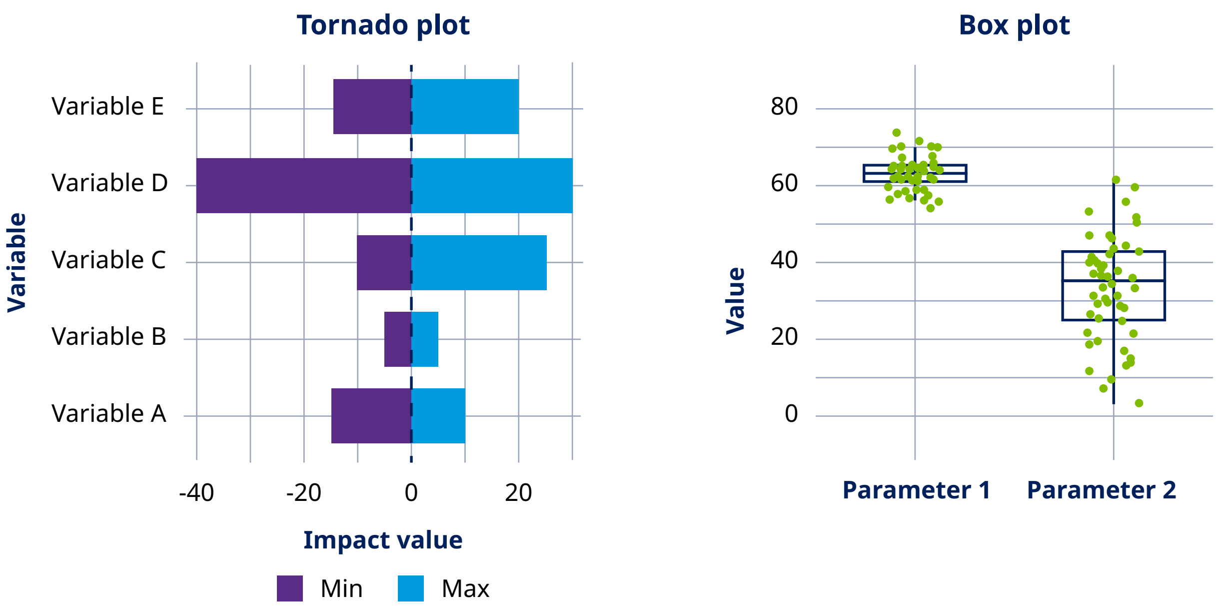
Confidence and uncertainty intervals are both estimates of the overall uncertainty, but they differ in what they represent and how they are calculated.

Confidence intervals represent the uncertainty in the true population parameter under a certain level of confidence. Uncertainty intervals also represent uncertainty in the population parameter but additionally consider other sources of uncertainty, including the model limitations and data quality.

To see the impact of a change in one parameter value (e.g. vaccine efficacy) on the outcomes, we can use the model to assess how much the model predictions change if we alter the value of that parameter while keeping all other parameters constant; this is called a one-way or univariate sensitivity analysis. Alternatively, we can change multiple parameters at the same this time; this is called a multiway or multivariate sensitivity analysis. Uncertainties can be calculated using either deterministic (without additional randomness) or probabilistic (with additional randomness) methods.

There are multiple ways to visualize uncertainty in parameter values or results. Modelling teams can display some statistical measures (e.g. range, 95% confidence or uncertainty interval, standard deviation, standard error). Some uncertainty visualization using graphs and charts are shown in *Figure A3.1.*

Fig. A3.1. Examples of visualizing uncertainty



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Annex 4

Model validation

Despite the inevitable uncertainty in a model, it is important to understand the overall validity of the model by assessing its quality and main drivers (assumptions or parameters) that influence the outputs. It is important to ask the following questions:

- Before projecting the future or future scenario analyses, is the model able to reproduce historic estimates of disease burden?
- What model inputs or assumptions have the greatest influence on the results?

Additional resources

Modelling methods for predicting epidemiological and health economic effects of vaccinations: guidance for analyses to be presented to the German Standing Committee on Vaccination (STIKO). Berlin: Robert Koch Institute; 2024 (https://www.rki.de/EN/Topics/Infectious-diseases/Immunisation/STIKO/STIKO-methodology/Guidance_for_analyses.pdf?__blob=publicationFile&v=1, accessed 20 October 2025).

Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Med Decis Making. 2012;32(5):733–743. https://doi.org/10.1177/0272989X12454579.

WHO guide for standardization of economic evaluations of immunization programmes, 2nd edition. Geneva: World Health Organization; 2019 (https://iris.who.int/handle/10665/329389. License: CC BY-NC-SA 3.0 IGO).

This overall process is often referred to as model validation. No specific checklist exists for model validity that should be applied to all models. Instead, each modelling exercise must determine what is important to evaluate and verify. There are several ways to approach model validation, depending on the availability of additional data or information and the specific modelling question, such as comparing estimated outcomes from the model with what is observed in the real world for epidemiologic plausibility, checking the accuracy of coding and data analysis, and comparing results from more than one version of the model.

Cross-validation is a common type of model validation that involves testing models on withheld data and seeing how they differ. These models may represent different versions of the same underlying model implemented by the modelling team in the specific modelling exercise, such as with different subsets of the dataset included, or across different values of the parameters. Alternatively, these models could include comparisons of external models. Multimodel comparisons, in which specific models are synthesized and compared to understand differences in outcomes and more comprehensively assess the evidence available for decision-making, are a special kind of cross-validation *(1)*.

It is important to consider how these validation exercises should be interpreted. Considerations might include:

- evaluating the rigour of the modelling progress;
- assessing the quantity and quality of the data used (e.g. how well they represent the model's proposed use);
- understanding the ability of the model to simulate scenarios in appropriate detail;
- observing how closely results match observed outcomes, including after making appropriate assumptions about uncertain elements or parameters;
- identifying the most important data to be collected based on an understanding of the key drivers of the model output.

After the validation exercises are complete, the project team should determine the appropriateness of the model and make any necessary adjustments. Validation contributes to the iterative nature of the modelling process.

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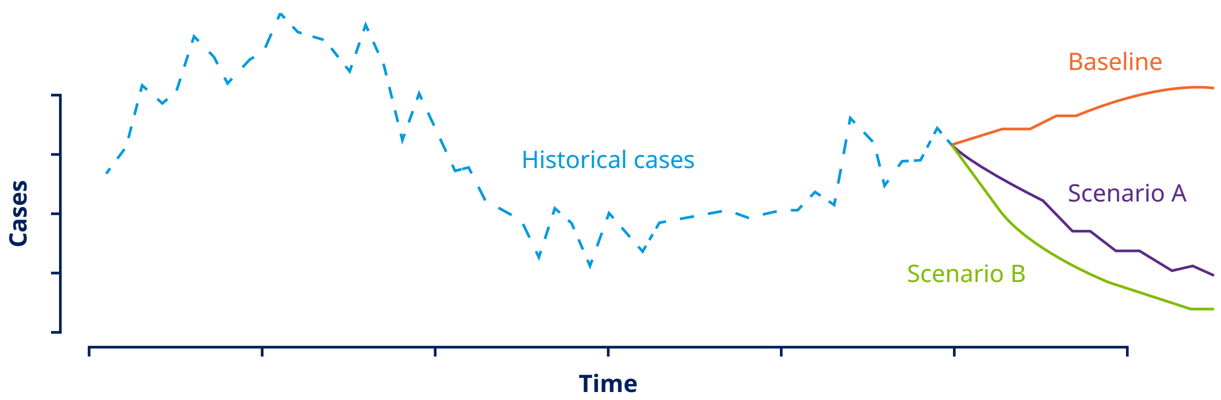
Annex 5

Scenario analysis

Once the validity of the model has been established, the modelling team can begin to assess future scenarios. Scenarios represent a range of potential futures or policy options for a given setting. For example, if a modelling question concerns the introduction of a new vaccine, different scenarios to consider may include *(Figure A5.1)*:

- no vaccine introduction (i.e. the current or baseline scenario, if nothing were to change);
- a recommendation with immunization targeted at every person in a defined age group (Scenario A);
- a recommendation with immunization targeted at every person in a defined age group plus a catch-up campaign for older people (Scenario B).

Fig. A5.1. Results from hypothetical scenario analysis



A hypothetical result of this scenario analysis is shown in Figure A5.1, which displays historical cases and results of three different scenarios: a baseline scenario to capture what would happen if no vaccine was introduced, and Scenarios A and B, in which different vaccine introduction strategies were implemented (i.e. targeted age groups). Results of models that accurately capture differences in these hypothetical scenarios can be compared to assess the impact or costs of these implementation strategies. Model scenarios should be discussed with the modelling team and relevant partners to be in line with the specific policy question to be addressed.

Although models are hypothetical depictions of the real world, they must be grounded in reality. Therefore, developing scenarios that are feasible and relevant to end-users is critical to ensure the relevance of the modelling results. If scenarios are impossible or impractical to implement in the real world (e.g. assuming a catch-up campaign will be able to achieve 100% coverage) or directly contradict known indications for the vaccination of interest (e.g. rubella vaccination campaigns among pregnant women), modelling results will be less useful.

Department of Immunization,
Vaccines and Biologicals
World Health Organization
20, Avenue Appia
1211 Geneva 27
Switzerland

9789240119550