Study Design Components of Economic Evaluation

Presented by Dr. Emmanuel Drabo
Overview

• Different types of models that can be constructed to perform cost-effectiveness analysis

• Outlining the study designs that contribute to information for constructing an economic model
## Standard Vaccine Cost-Effectiveness Analysis Scenario:
Infant/Child Malaria Vaccine

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Cost</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>New malaria vaccine</td>
<td>• Vaccine costs</td>
<td>• # malaria cases averted</td>
</tr>
<tr>
<td></td>
<td>• Administration costs</td>
<td>• # infant deaths averted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DALYs averted</td>
</tr>
<tr>
<td>Long-lasting, insecticide-treated nets (LLITN)</td>
<td>• LLITN costs</td>
<td>• # malaria cases averted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• # infant deaths averted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DALYs averted</td>
</tr>
<tr>
<td>Do nothing: treat acute malaria cases</td>
<td>Medical cost</td>
<td>• # malaria cases averted</td>
</tr>
<tr>
<td></td>
<td>Non-medical direct cost</td>
<td>• # infant deaths averted</td>
</tr>
<tr>
<td></td>
<td>Indirect costs</td>
<td>• DALYs averted</td>
</tr>
</tbody>
</table>
Creating a Decision Analysis Framework

• Points to consider in framework construction:
  • Not every infant receiving an intervention will have similar outcomes/respond equally
  • Possible outcomes following vaccination:

Vaccination programme

- Vaccinated and no immunity
  - Severe malaria
  - Mild malaria
  - Death

- Vaccinated and partially immune
  - Severe malaria
  - Mild malaria
  - Death

- Vaccinated and fully immune
  - Full recovery
  - Death
Decision Analysis

• Uses mathematical relationships to describe a series of possible infection consequences that could flow from a vaccine program, or lack thereof

• Is a systematic approach to decision-making that accounts for *variability* and *uncertainty* in Vaccine outcomes

• Variability
  • is the likelihood of responding differently to a Vaccine intervention
  • probability of disease infection with or without vaccine

• Uncertainty
  • estimation of probabilities are uncertain
  • Unintended consequences of vaccine use and investment
  • accounted for using sensitivity analyses
Decision Analytical Models

• Decision analytical models are structured
  • to characterize outcomes of vaccines and alternative options
  • is done in a way that is appropriate for the infectious disease condition and vaccine usage
  • to represent clinical/disease pathways that are pertinent to the infection, or pathways avoided with vaccine use

• Allows the synthesis of evidence from a variety of sources to estimate vaccine costs, safety and effectiveness
Decision Analytical Models

• Can allow for events reoccurring over time
  • Reinfection
  • Disease progression
  • Vaccine program completion

• Allows an assessment of different types of uncertainty
  • Unintended consequences of vaccine use
  • Unknown vaccine effectiveness

• Examples of decision analytical models include:
  • Decision tree
  • Markov model
Decision Tree

Possible pathways for a vaccination program against rotavirus compared to no vaccination
**Decision Tree: Hib Vaccine**

*Cycle repeated for 15 birth cohorts (2010-2024)*

**Figure 1** Model structure for cost-effectiveness of Hib vaccine in Haryana State, India.

*Notes: NPNM = non-pneumonia, non-meningitis; PHC = primary health centre*
Decision Tree vs. Markov Model

**Decision tree**
- Consists of pathways representing different **sequence of events**
- Chance (circular) nodes show a point where two or more alternative events are possible
- Pathways are mutually exclusive events
- Probabilities show the likelihood of an event occurring at a chance (circular) node

**Markov model**
- Represents a set of possible transitions between different **disease states** which evolve over time
- Disease states are mutually exclusive
- Transition probabilities determine
  - the direction and
  - speed of transition between disease states
<table>
<thead>
<tr>
<th>Decision tree</th>
<th>Markov model</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Suitable for ‘once-only’ infectious diseases</td>
<td>• Suitable for handling the progression of infectious disease</td>
</tr>
<tr>
<td>• Less suitable for longer-term outcomes</td>
<td>• Can handle recurring events (e.g. reinfection)</td>
</tr>
<tr>
<td>• possible to add branches (not efficient)</td>
<td></td>
</tr>
<tr>
<td>• But can become unwieldy</td>
<td></td>
</tr>
<tr>
<td>• Difficult to handle recurring events</td>
<td></td>
</tr>
</tbody>
</table>
Probabilities (a, b and c) describe the likelihood of an infant experiencing one of three possible outcomes following vaccination:

- **Vaccinated and no immunity** with probability \(a\)
- **Vaccinated and partially immune** with probability \(b\)
- **Vaccinated and fully immune** with probability \(1 - (a + b)\)

**Infant vaccinated**
Probabilities

• Probabilities are important parameters in the decision analytical model

• They are defined as:
  • The number of individuals who experience an event out of the entire population being studied =
    
    \[ \frac{\text{(\# of people with an event)}}{\text{(total \# of people at risk for the event)}} \]

  • People must be at risk for the event
  • Prevalence is a probability (or proportion)
  • Probabilities must range between 0 and 1

• Example: if out of 100 infants at risk of developing diarrhoea, 11 cases are detected, the probability of developing diarrhoea →

  \[ \frac{11}{100} \rightarrow 0.11 \]
Sources of Probability Estimates

• Probabilities can be obtained from a variety of sources

• These sources typically provide estimates of vaccine efficacy

• Vaccine efficacy = intended impact on measurable end-points
  
  • Biological markers (e.g. level of detectable antibodies below a defined threshold)
  • Clinical disease stages
    • mild clinical cases
    • severe clinical case
    • physician consultations
    • Hospitalizations
    • Mortality
    • Asymptomatic
Sources of Probability Estimates

• Observational studies
  • Cohort studies
  • Case-control studies
  • Cross-sectional studies

• Experimental studies
  • Randomized control trials (RCTs)
  • Non-randomized trials
  • Quasi-experimental designs

• Systematic Reviews and Meta-Analyses
Difference Between Experimental and Observational Studies

Did investigator assign exposures?

Yes

- Experimental study
  - Random allocation?
    - Yes: Randomised controlled trial
    - No: Non-randomised controlled trial

No

- Observational study
  - Comparison group?
    - Yes: Analytical study
    - No: Descriptive study

Direction?

Exposure → Outcome

- Exposure and outcome at the same time
  - Cohort study
  - Case-control study
  - Cross-sectional study
Observational studies

• Cohort studies:
  • a group of 2 cohorts (exposed and unexposed to an intervention) at risk of an event are followed forward for a given period of time
  • Enables calculation of incidence rates

• Case-control studies
  • Starts with an outcome, such as disease, and looks backward in time for exposures that might have caused the outcome

• Cross-sectional studies
  • Both exposure to the intervention and the measurable end-point are ascertained at the same time
  • Can be used to estimate prevalence/probabilities
Temporal Direction of Observational Studies

- **Cohort study**: Exposure → Outcome
- **Case-control study**: Exposure ← Outcome
- **Cross-sectional study**: Exposure ↔ Outcome

[Diagram showing the temporal direction of various observational studies]
Randomized-Control Trials (RCTs)

• Are often regarded as the gold standard for determining vaccine efficacy
• An important feature of RCTs is the assignment of participants to exposures purely by the play of chance.
  • This reduces the likelihood of bias in determining outcomes
  • When properly implemented, random allocation precludes selection bias.
• Are especially useful for examination of small or moderate effects.
Limitations of RCTs

• Generalizability and extrapolation to different settings can be limited by variations in the biological properties of the virus and other contextual factors.

• For example,
  • Transmission of infection is influenced by contextual factors such as
    • How frequently people interact,
    • Biological transmissibility under the influence of climate
  • People are infected by different “variations” of the same pathogen in different parts of the world resulting in differences in the associated clinical disease and health care utilization.

• Cost of conducting a RCT often run into tens of millions of US dollars.
Systematic Reviews and Meta-Analyses

- Source estimates of vaccine efficacy for economic evaluation should preferably be based upon
  - Systematic reviews of the available literature or
  - Meta-analyses
Systematic Review and Meta-Analysis

What’s the difference?

• Systematic Review
  • A literature review focused on a research question that tries to identify, appraise, select and synthesize **ALL** high quality research evidence relevant to that question
  • Support evidence-based vaccine use with studies from randomized controlled trials (RCTs) or observational studies (e.g. case-control or cohort)

• Meta-Analysis
  • The statistical combination of results from two or more separate studies
  • Can be accomplished following a systematic-review
When Are Systematic Reviews Needed?

• When an important vaccine research question needs to be addressed
  • Gaps in the literature or conflicting results between studies, countries where vaccine is used

• When there is uncertainty regarding an intervention
  • Uncertainty may lie in:
    • Population, Vaccines, Outcomes

• When several primary studies exist
  • Lack of strong evidence
Why Are Systematic Reviews Needed?

• Too much information
• Not enough time
  • More than 2 million articles published yearly from more than 200 biomedical journals
  • Results can often be contradicted by subsequent vaccine trials

• Taken together, a clearer picture can emerge
  • Minimize biases
  • Increase statistical power
  • Improve generalizability
  • Improve allocation of resources for other needed trials = minimize funding of unnecessary trials
Finding All Relevant Studies: Sources

- Electronic databases
  - MEDLINE (Ovid/PubMed)
  - Cochrane Library
  - EMBASE
  - PsychINFO
  - CINAHL
  - UK NICE
  - WHO Vaccines

- Hand searching
  - Reference lists of trials and/or reviews
  - Journals

- Sources for unpublished information
  - FDA website
  - Clinical Trials.gov
  - Registries

- Industry dossiers
Limitations Of Systematic Reviews

• Only as good as what is available and what is included
  • Issue of publication bias
    • Restricted to published results
  • Quality of individual trials
    • “Garbage In, Garbage Out”

• Good quality systematic reviews typically do not address all the issues relevant for decision making
  • Evidence outside the scope of the review may be relevant and needed for decision making
  • Cost and implementation implications may not always be addressed
Limitations Of Systematic Reviews

• Unrealistic expectations
  • What if results conflict with a good quality large vaccine trial?
  • About 10-23% of large trials disagreed with meta-analyses*

• May not always include the most up to date studies
  • When was the last literature search conducted?
  • Estimate: 3-5 years**

• Does not make decisions for the vaccine recipient
  • These are not guidelines
  • The reader uses their own judgment

Meta-analysis

Is combining results of individual studies appropriate?

• The review should provide enough information about the included studies for you to judge whether combining results was appropriate.

• Two types of heterogeneity
  • Clinical heterogeneity
    • Does it make clinical sense to combine these studies?
  • Statistical heterogeneity
    • Are there inconsistencies in the results?
    • Calculation of Q-or I-squared statistic

• Common sources of heterogeneity
  • Clinical diversity between studies, conflicts of interest, and differences in study quality
Data Synthesis

• Quantitative or **meta-analyses**
  • Statistical method for combining results from >1 study
    • Advantage: provides an estimate of treatment effect
    • Disadvantage: misleading estimate if used inappropriately
• Misuse of terminology
  • **Systematic review and Meta-analysis = NOT the same**

Adapted from Cochrane Collaboration open learning materials for reviewers 2002-2003.
Calculating incidence rate

• Incidence rate = \( \frac{\text{Number Of Cases}}{\text{Number Of Person-time}} \)

• In this study
  • Number of malaria cases = 3
  • Number of person-days = 236

• Incidence rate \( \Rightarrow \) \( 3 \div 236 = \)
  0.0127 cases per person day
  or 1.27 cases per 100 person-days
  or 12.7 cases per 1000 person-days
  or etc...
### Calculating incidence rates

- **How many new cases of malaria at the end of 5-year follow-up?**
  - Answer: 3

- **What is the # of person-years?**
  - Answer: $2.5 + 5 + 1.5 + 5 + 0.5 \Rightarrow 14.5$ person-years

- **What is the incidence rate?**
  - Answer: $\frac{3}{14.5}$
  - $\Rightarrow 0.207$ cases per person year or 20.7 cases per 100 person years
Estimating Parameters for COVID-19 pandemic

• Limited information available, especially from still ongoing RCTs
• Explore regularly published reports and datasets from:
  • WHO
  • Government/MoH
  • JHU
  • Local universities
  • Verifiable news reports