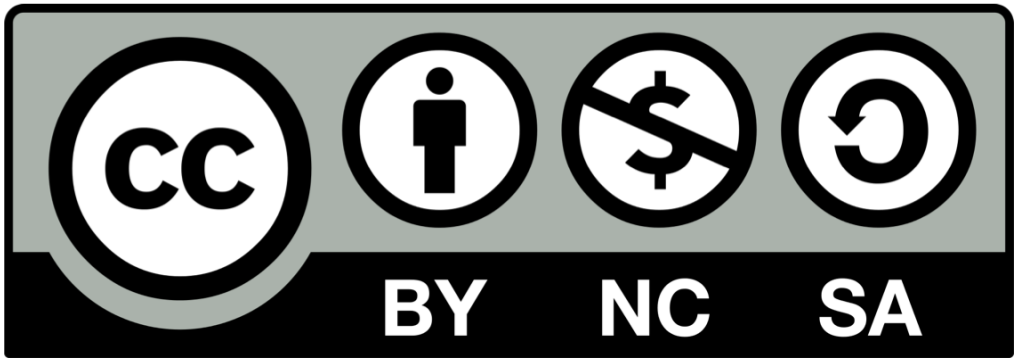
Economic Evaluation

Study Design Components of Economic Evaluation

TVEE
TEACHING VACCINE ECONOMICS EVERYWHERE

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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
- How to input source probabilities into a simple decision tree model

Objectives

- To differentiate between uses of decision tree and Markov model
- To identify study designs that contribute to better cost, effectiveness and probability parameter estimates
- To understand the process of probability extraction from high-quality sources

Standard Vaccine Cost-Effectiveness Analysis Scenario: Infant/Child Malaria Vaccine

Intervention(s)	Cost	Benefits
New malaria vaccine	• Vaccine costs • Administration costs	• # malaria cases averted • # infant deaths averted • DALYs averted
Long-lasting, insecticide-treated nets (LLITN)	• LLITN costs	• # malaria cases averted • # infant deaths averted • DALYs averted
Do nothing: treat acute malaria cases	Medical cost Non-medical direct cost Indirect costs	• # malaria cases averted • # infant deaths averted • DALYs averted

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

Vaccinated and partially immune

Vaccinated and fully immune

Severe malaria

Mild malaria

Death

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

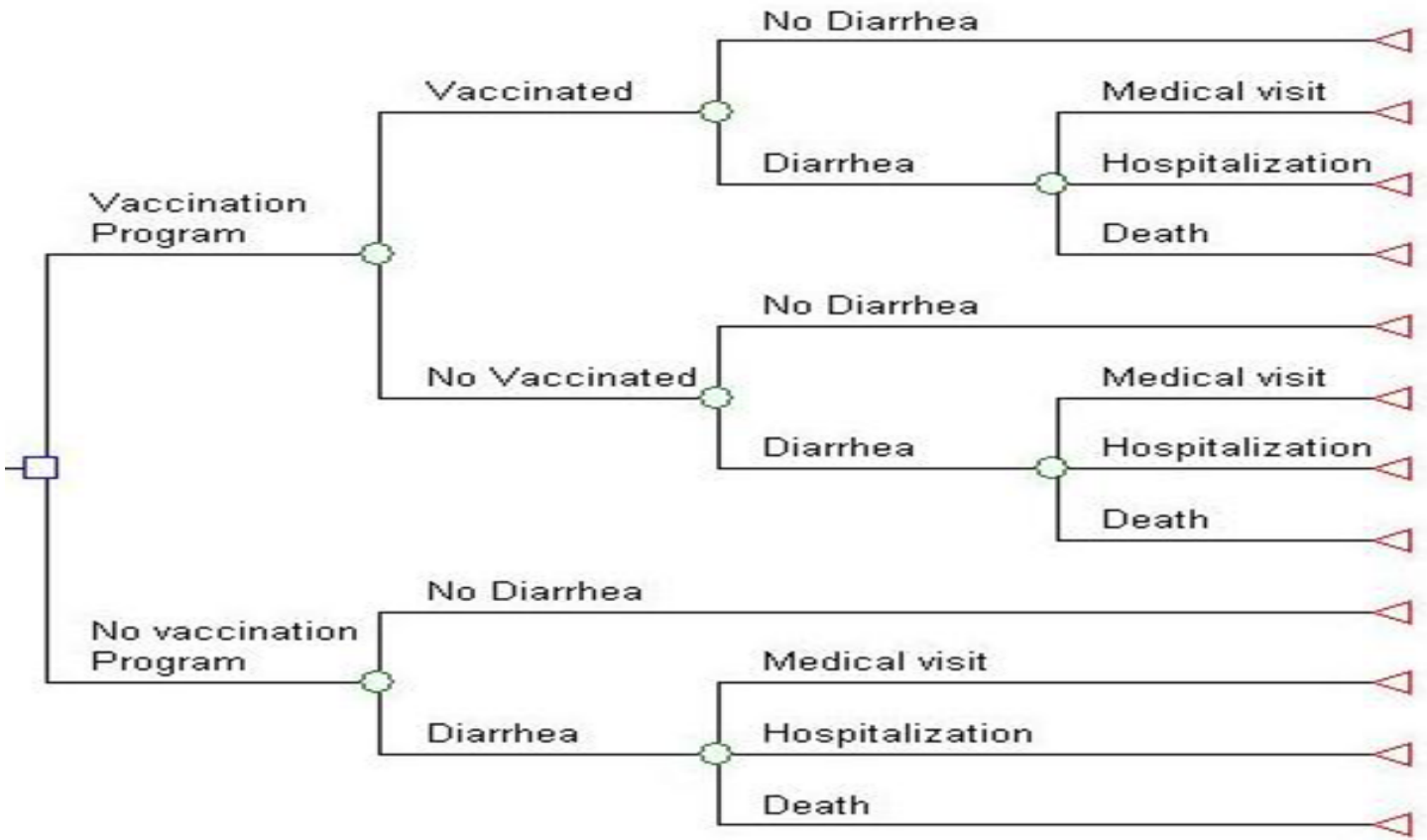
Decision Analytical Models

- 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

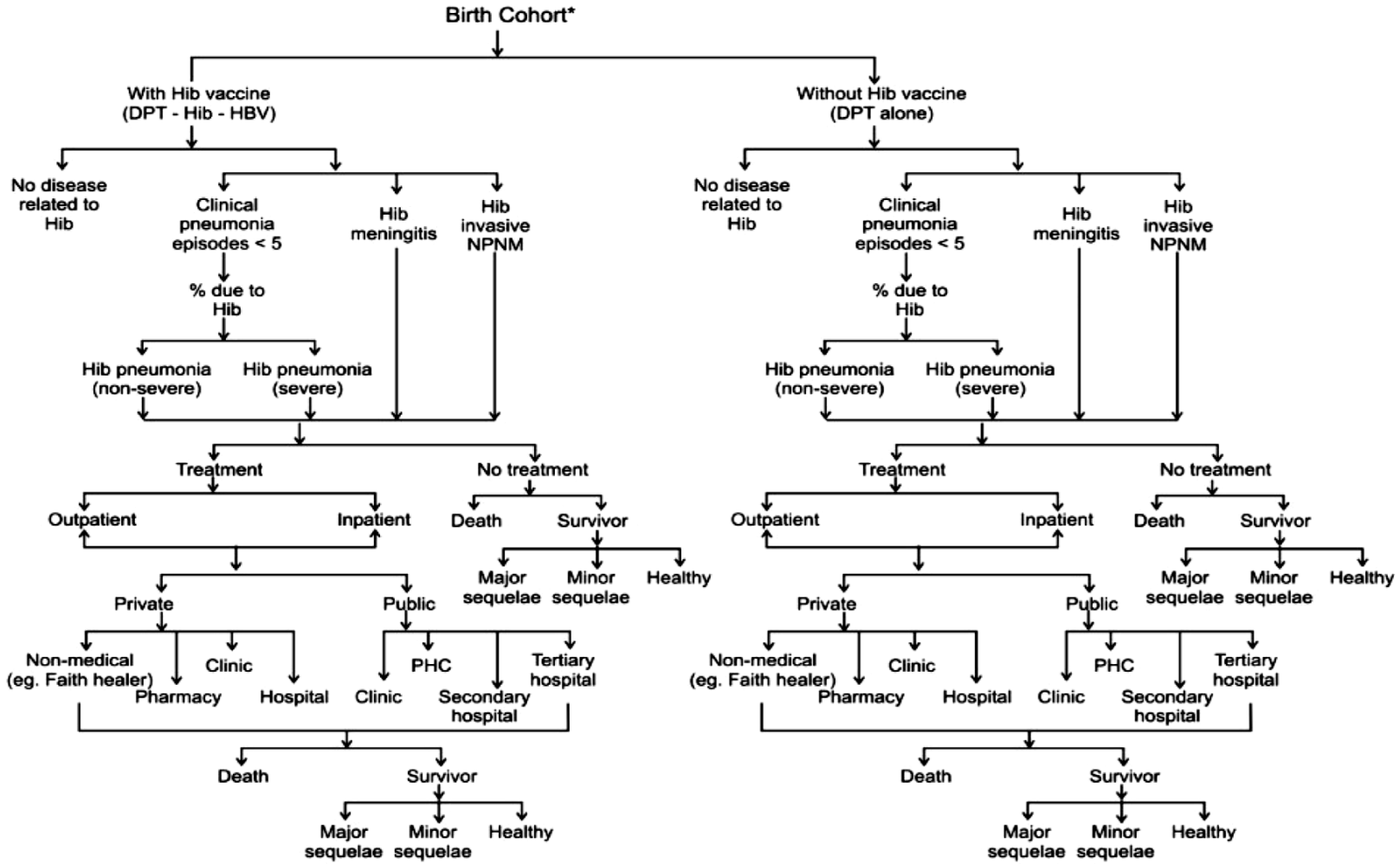
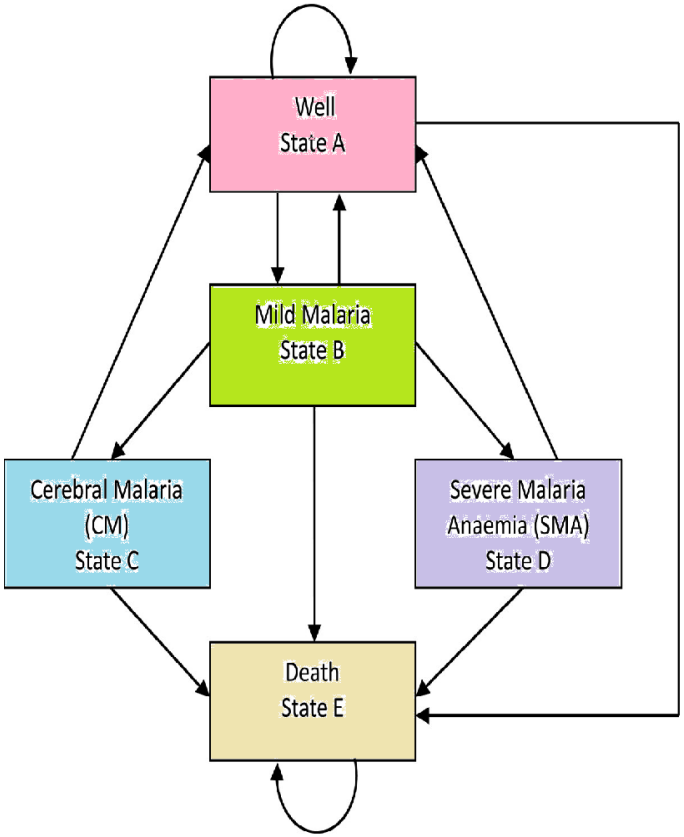


Figure 1 Model structure for cost-effectiveness of Hib vaccine in Haryana State, India
Notes: NPNM=non-pneumonia, non-meningitis; PHC=primary health centre

Gupta et al. 2013

Markov Models



Decision Tree vs. Markov Model

Decision tree

- Consists of pathways representing different **sequence of events**
- Chance (circular) nodes shows 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

Decision tree vs. Markov model

Decision tree

- Suitable for ‘once-only’ infectious diseases
- Less suitable for longer-term outcomes
  - possible to add branches (not efficient)
  - But can become unwieldy
- Difficult to handle recurring events

Markov model

- Suitable for handling the progression of infectious disease
- Can handle recurring events (e.g. reinfection)

Probabilities

Probabilities (a, b and c) describe the likelihood of an infant experiencing one of three possible outcomes following vaccination



Infant vaccinated

a

Vaccinated and no immunity

b

Vaccinated and partially immune

$1 - (a+b)$

Vaccinated and fully immune

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 =

    (# of people with an event) / (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 ➔

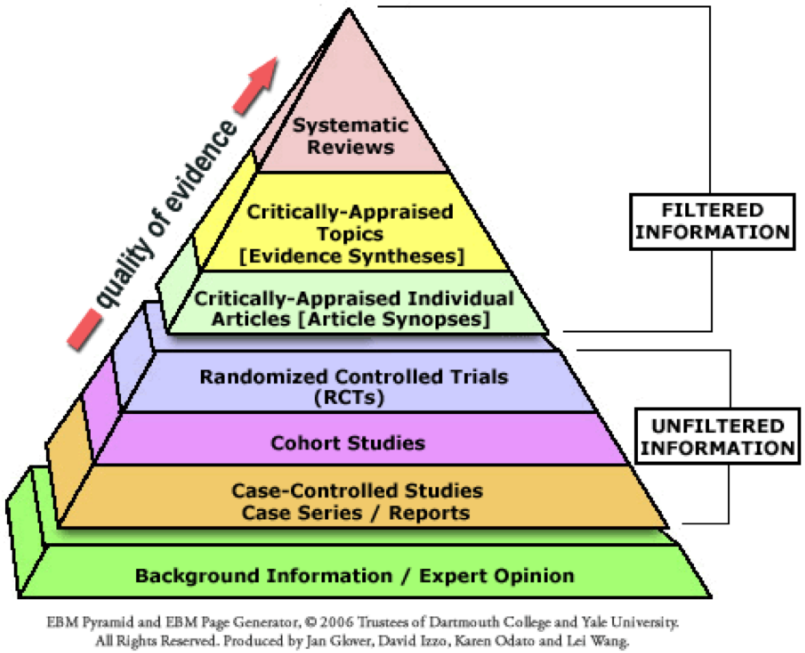
  11 ÷100 ➔ 0.11

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

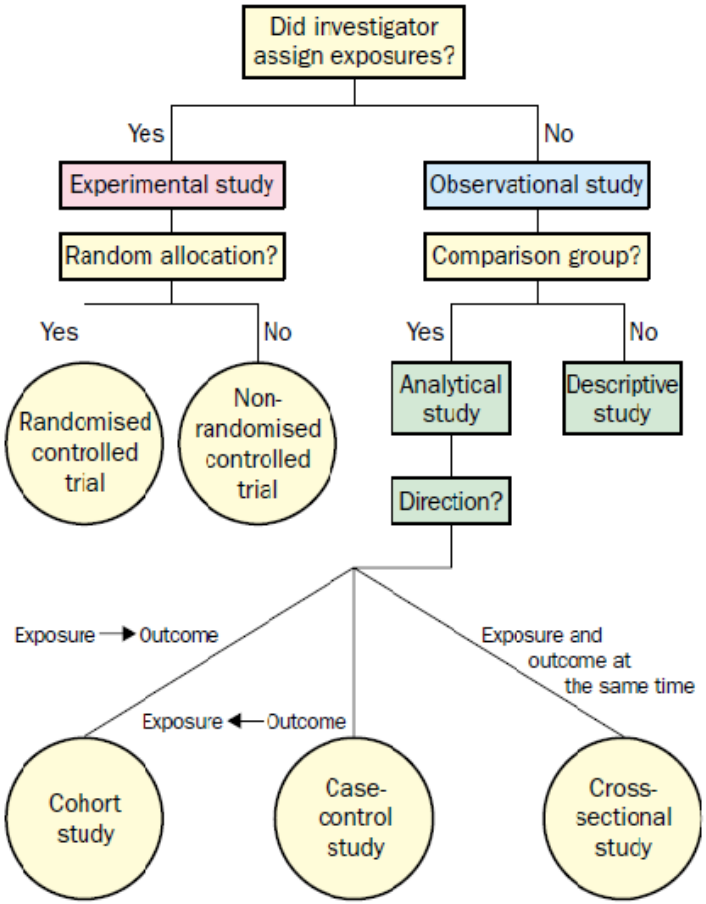
Sources of Probability Estimates

- 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



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Difference Between Experimental and Observational Studies



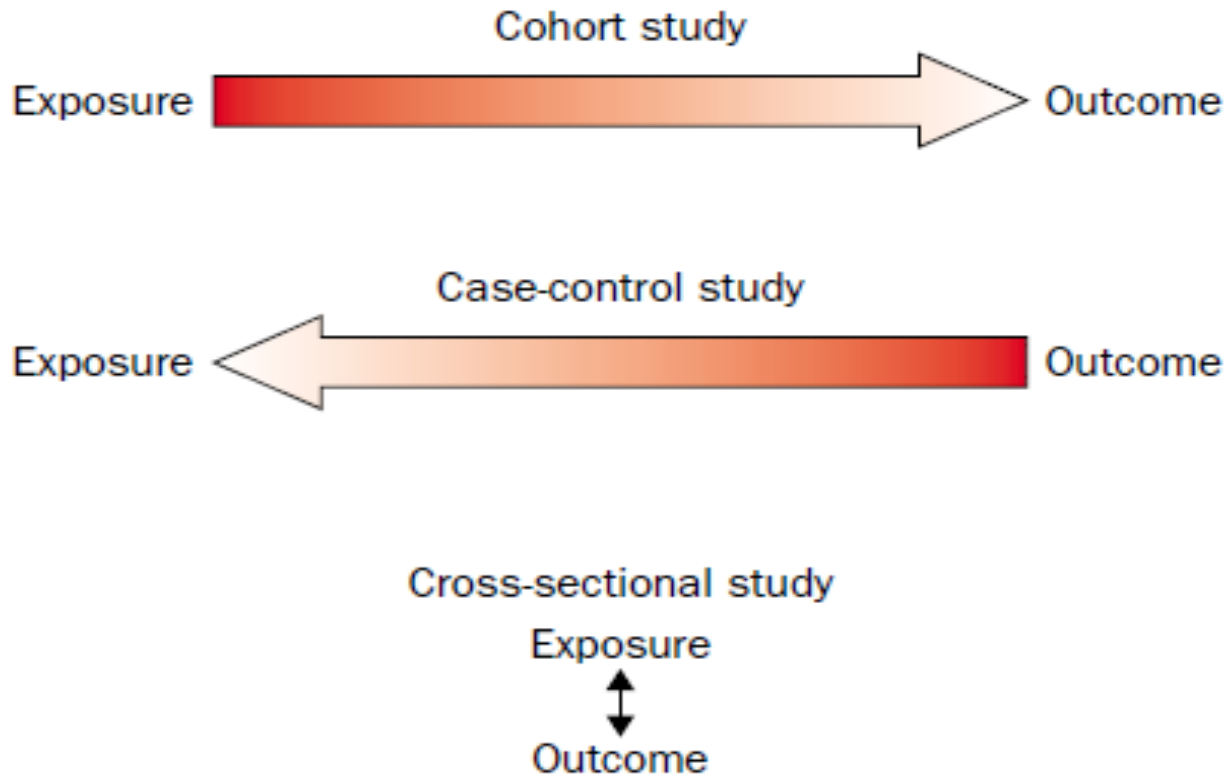
Observational studies

- 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



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?

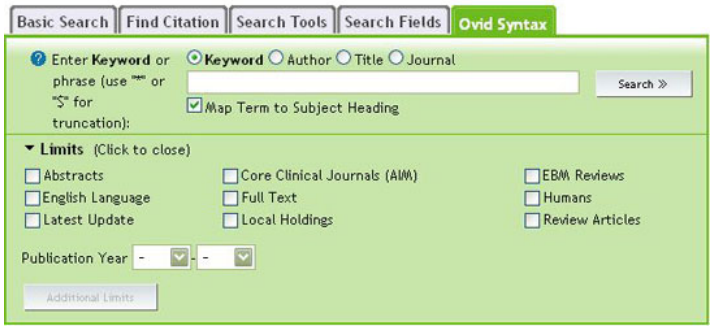
- When an important vaccine research question needs to be addressed
  - Gaps in the literature or conflicting results between studies, countries where vaccine is used
- When there is uncertainty regarding an intervention
  - Uncertainty may lie in:
    - Population, Vaccines, Outcomes
- When several 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



NCBI

PubMed www.pubmed.gov

A service of the U.S. National Library of Medicine and the National Institutes of Health

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



THE COCHRANE COLLABORATION®

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

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

- Industry dossiers

PhRMA

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*

*Ioannidis, et al. JAMA 1998; 279:1089-93. **Shojoania, et al. Ann Intern Med 2007; 147:224-33.

Meta-analysis

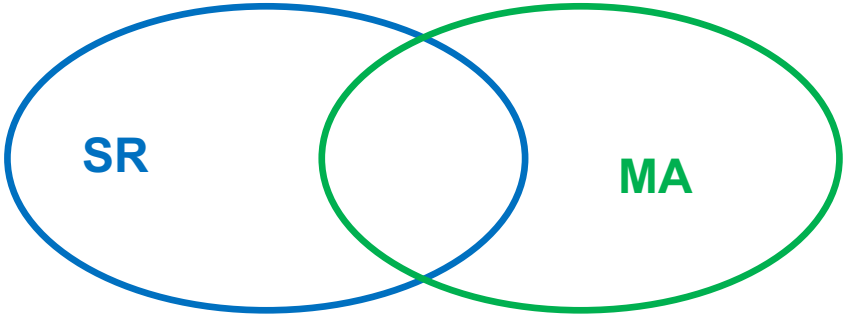
Is combining results of individual studies appropriate?

- 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 = <u>NOT</u> 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 ➔ 3 ÷ 236 =

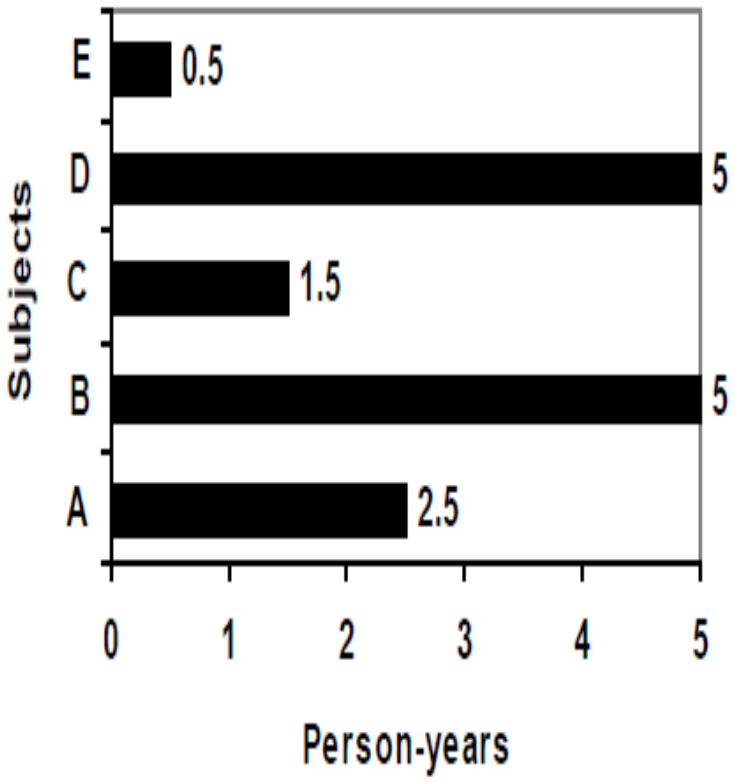
  0.0127 cases per person day

  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 ➔ 14.5 person-years
- What is the incidence rate?
  - Answer = 3/14.5

  ➔ 0.207 cases per person year or 20.7 cases per 100 person years

Exercise: CEA Study Design

- Review questions in groups
- Discuss potential responses
- Respond to questions online

Discussion Questions (Quiz)

1. What is the gold standard study design from which to extract probabilities of vaccine effectiveness
   a. Randomized Clinical Trial (RCT)
   b. Cohort Study
   c. Case-Control
   d. Case Series

2. Which is a better reflection of multiple studies' results of vaccine effectiveness
   a. Meta-Analysis
   b. A single, well done RCT
   c. Cohort Study
   d. Case-Control

3. Which study design provides the most generalizable results based on the use of data of patients in the real-world
   a. RCT
   b. Cohort Study
   c. Case Series

4. Which modeling approach is better to represent the likelihood of disease reinfection over multiple years, requiring continuous re-vaccination (e.g. for influenza
   a. Decision Tree
   b. Markov Model