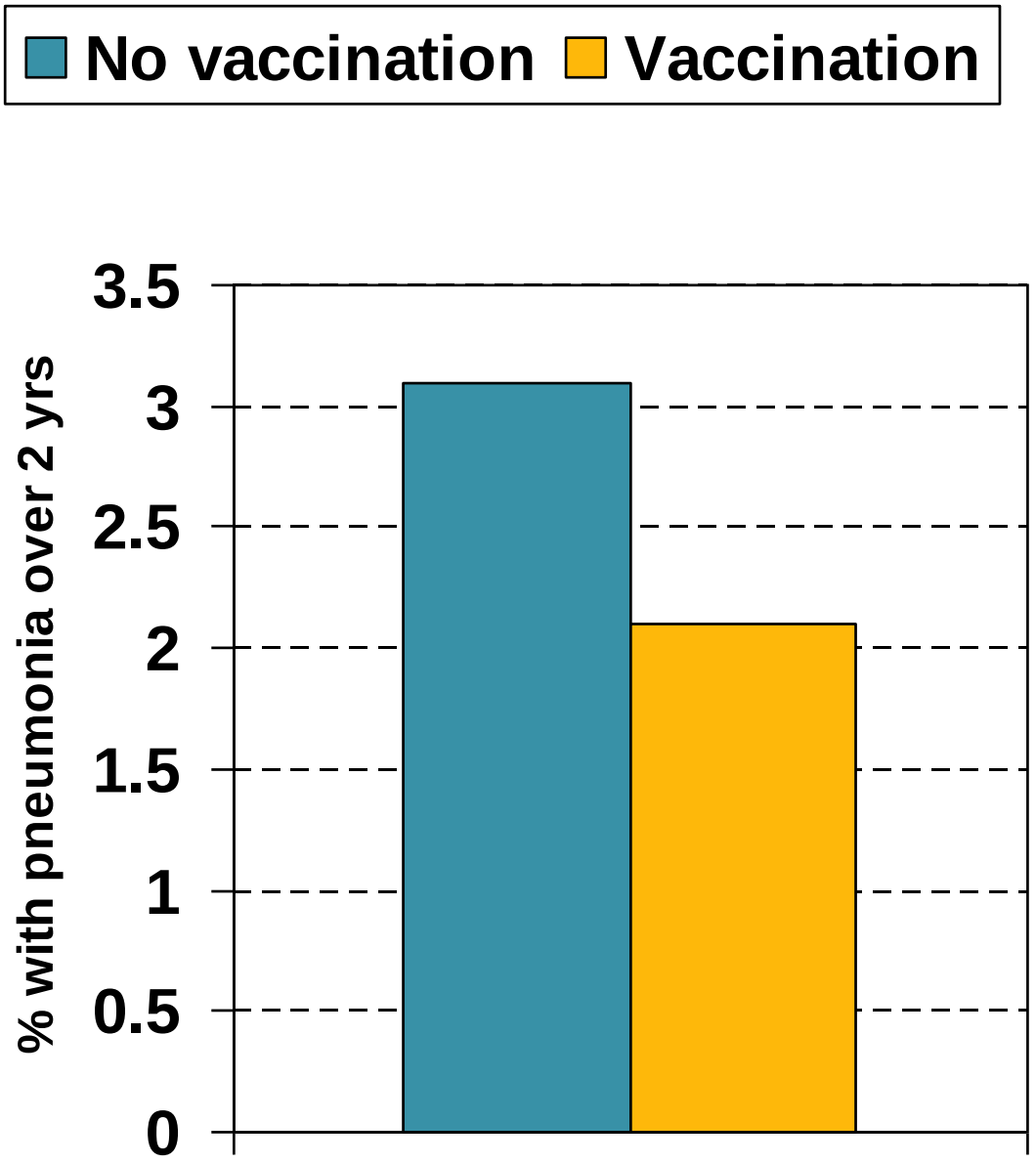
# Intervention studies

# Example


No vaccination
Vaccination
% with pneumonia over 2 yrs
3.5
3
2.5
2
1.5
1
0.5
0

# Basic features of intervention studies

- An intervention study involves an intentional change in some aspect of environment or status of the subjects of the investigation.
- Intervention studies differ from observational studies in that the researcher seeks to compare two or more groups that differ as a result of deliberate action rather than natural or found variation.

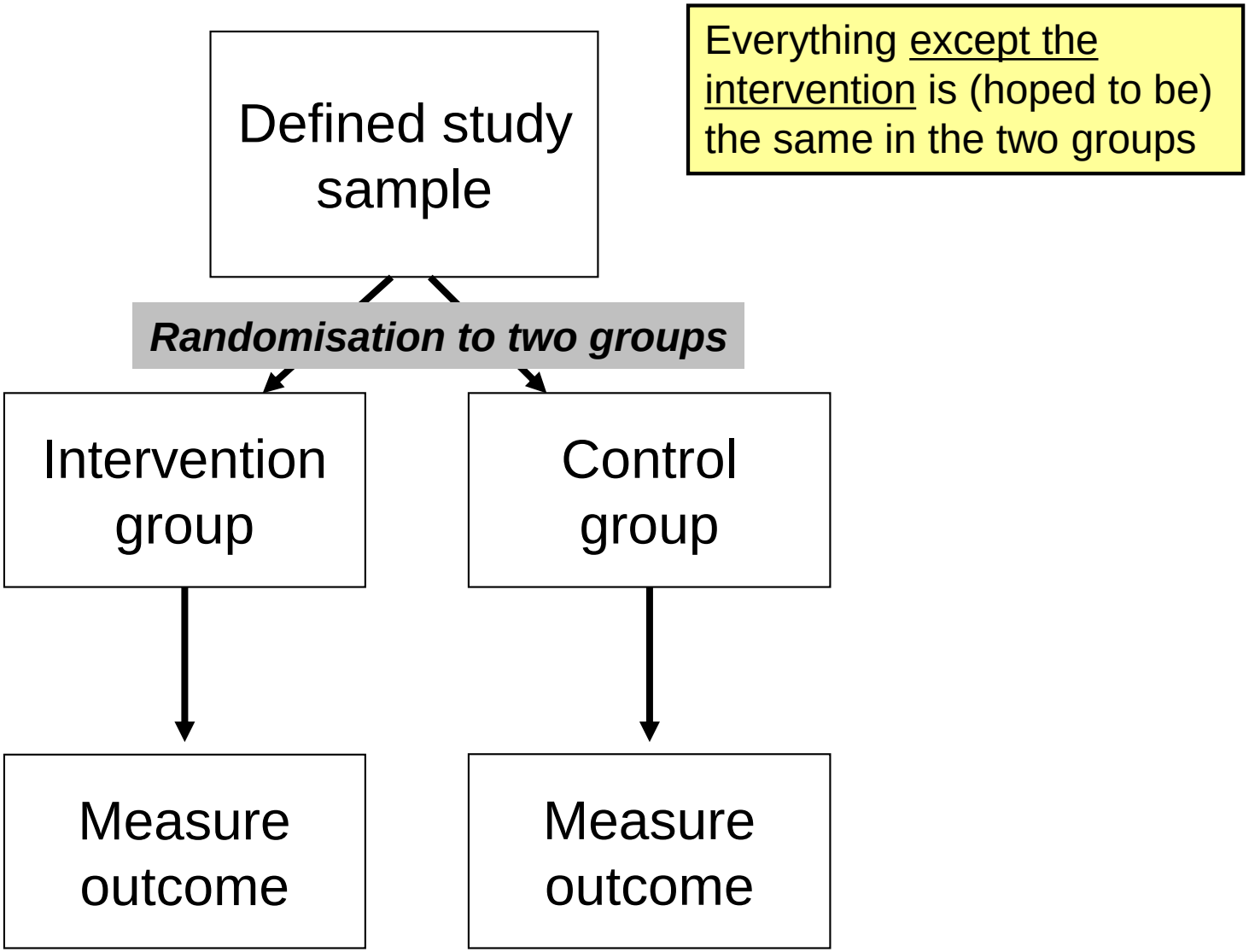
# Observational vs. Intervention studies

What is the difference between observation and intervention studies?

- Both can be used to compare differences between groups
- Intervention studies involve exactly what they say; there is an intervention in one of the groups (at least). So, the research team does intervene rather than just observe the study participants

# Main principle of intervention studies

- A **randomised controlled trial** is a type of experiment.
- *In simple form*, the participants are distributed on a strictly random basis into two groups that do not differ in number or quality: the control and intervention groups.
- The **control group** receives no intervention or inactive or PLACEBO intervention or the "routine" care.
- The **intervention group** receives one single uniform intervention that we are testing.
- Groups should be equal apart from variable under test
- If the **condition** of the two groups **differs at the end** of the trial, then it **can only be the result of the intervention**.


Everything except the intervention is (hoped to be) the same in the two groups
Defined study sample
Randomisation to two groups
Intervention group
Control group
Measure outcome
Measure outcome

# Key issues in RCTs

- Careful entry criteria
- Assessment (Pre- & Post-intervention)
- Randomisation
- Allocation Concealment
- Blinding (Masking)
- Contamination
- Analysis – ITT
- Interpretation

# Entry criteria

- Aim in any research is to draw conclusions about a population from a sample
- Representative sample

**BUT**

- In RCT participants often have a disease
- Participants must be able and willing to take part
- Compromise: exclusion criteria *vs.* ideal sample

# Assessment

## OUTCOME

- Careful selection of outcome
- Careful measurement of outcome
  - Reliability and responsiveness
  - Baseline assessments may inform participants

## TIMING

- Sufficiently long after intervention to allow it to work
- Not so far after intervention that effect is lost
- Multiple follow ups
  - Variation / change over time (short-term vs long-term)

# Randomisation

- … is allocation of the units of analysis to the different experimental groups or conditions according to chance, such that each unit has an **equal probability of selection into each group**
- Most powerful way of ensuring characteristics **not** systematically allocated to a particular group
- Can randomise in groups (clusters)

# The aim of randomisation is to…

create groups that are comparable with respect to known or unknown confounding factors

There are two steps in the process

1. Generating an **unpredictable** allocation sequence e.g. tossing a coin, using a computer random number generator
2. Concealing the allocation sequence from the investigators

Not always possible

# Allocation concealment

- … is making sure that neither investigator nor patient can predict group assignment

**Adequate methods**

Off-site randomisation e.g. needing a phone call

Sequentially numbered, sealed, opaque envelopes

# Blinding

- If participants or researchers know whether participant is receiving intervention then there is risk of:
  - Measurement error
  - Different investigations & care study group etc.
  - Acceptability bias (Researchers influence participants behaviour)
- Different "levels" of blinding: can blind participants, researchers and/or statisticians or none

# "Levels" of blinding in interventions

**Single blinding**: If participants cannot be blinded to group allocation, as in behavioural trials (e.g. dietary advice), allocation and assessment of the outcomes should be concealed from researchers

**Double blinding**: neither researcher nor participant knows which of the study groups the participant has been allocated to (e.g. high quality drug trials)

**Triple blinding**: as for the double blinding but additionally the statistician is blinded

**Open RCT**: no blinding

# Allocation concealment vs. Blinding: is there any difference?

- Allocation concealment: neither investigator nor participant can **predict** group assignment
- Blinding: neither investigator nor participant **knows** which group the participant is assigned to (double blinding); single blinding if only investigator (or, in some cases, participant) is blinded
- How can you achieve this?
  - Allocation concealment: off-site randomisation
  - Blinding is not always feasible

# Contamination

- … occurs when the behaviour of the participants in one group is influenced by what happens in another group

- It is particularly a problem in evaluation of health education and community interventions.

# Analysis

- Simple - randomisation reduces risk of confounding
- Compare groups at baseline to see if they are broadly similar (no need for statistical tests)
- Compare groups at follow-up to estimate effect (statistical tests)
- Must consider all, not only those completed the RCT
- Intention to Treat (ITT) analysis
  - Analyse all according to baseline allocation
  - Even if participants didn‘t receive intervention
  - Minimise loss to follow-up or substitute data

# Interpretation of findings

- In any controlled trial, there is a **comparison group** that controls for (takes account of) background risk and extraneous variation in the outcome of interest and allows the effect of the intervention to be quantified. This can be done via:
- **Incidence risk/rate: ratio or difference** between intervention and control groups
- **Changes in prevalence: ratio or difference** between the intervention and control groups

# Challenges in RCTs

General points

- Complex to set up and administer
- Must account for many variables
- Some require long follow up
- Difficult with long-term interventions
- Difficult for uncommon health gains or uncommon adverse effects
- Potential loss to follow up

# Generalisability (*External validity*)

- Extent to which findings applicable to wider population
- High degree of control within RCT may restrict generalisability
- Specific population may not represent general population (e.g. willing volunteers)

# Advantages of RCTs

- Experimental: groups treated similarly except intervention
- Randomisation: characteristics similarly distributed
- Blinding
  - patients
  - investigators
  - statisticians

**Tells us that difference at the end is only due to intervention**

- ITT analysis

**Prevents attrition bias**

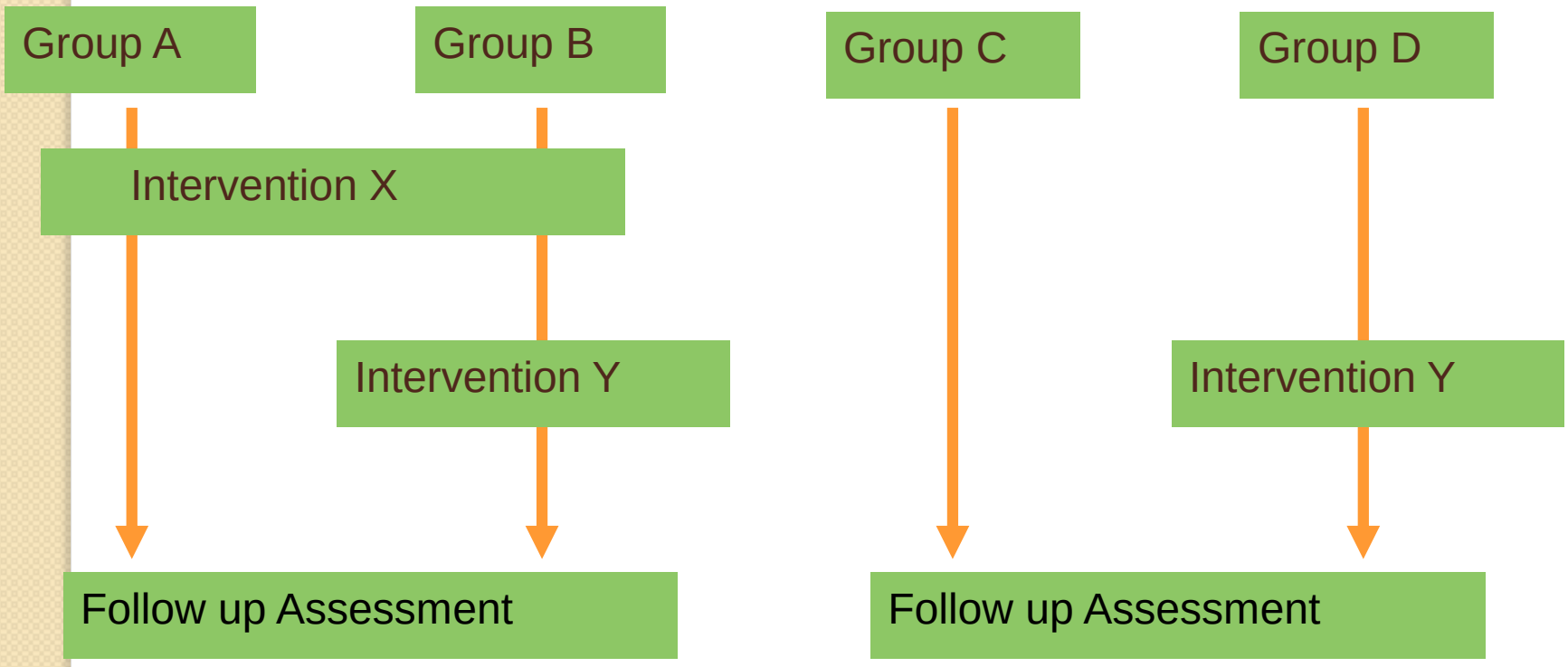
**Gold-standard epidemiological study design to assess effectiveness of interventions**

# Special types of RCT

- **Factorial design**
  - Tests cumulative effect of two or more interventions
- **Cross-over design**
  - All participants receive all treatments & act as own controls
- **Community-based Trials**
  - Intervention assigned to groups (randomise schools to treatment and control groups)
- **Complex interventions**
  - Many components, difficult to disentangle their effects

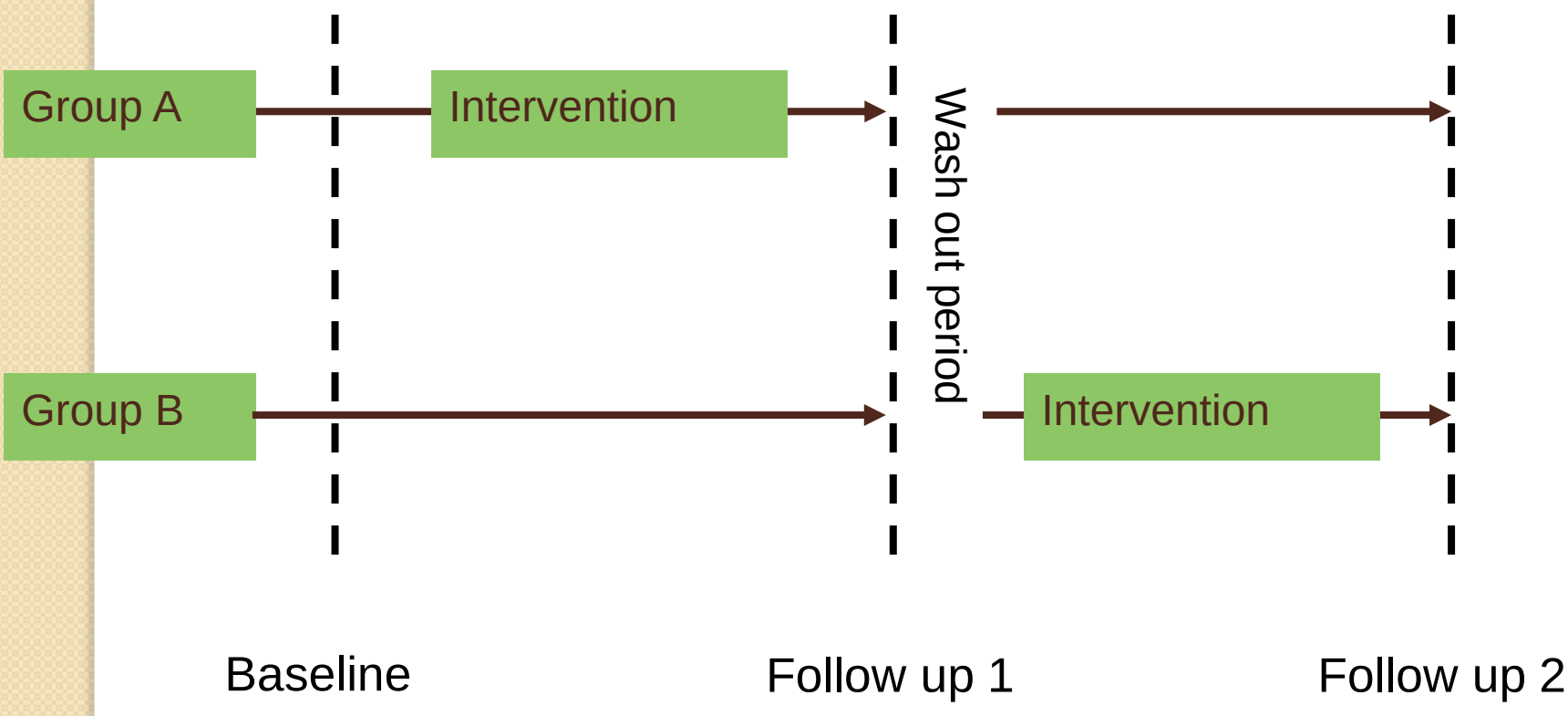
# Factorial design

**Tests cumulative effect of two or more interventions**



# Cross-over trial

**All participants receive all treatments & act as own controls**



# Complex intervention

"comprises a number of separate elements which seem essential to the proper functioning of the intervention although the active ingredient of the intervention that is effective is difficult to specify"

MRC definition (2000)

# Intervention studies: less powerful options

- ✓ **Are there any other studies (apart from RCTs) that may be classified as interventions?**
  - ***Quasi-experimental trial***
    - Non-random allocation to intervention and control groups
    - Patient or physician preference or other (convenient) way
    - Concerns about internal validity (non-comparable groups)
  - ***Intervention (non-controlled) studies***
    - Single group with assessments before and after intervention
    - V weak design as can't attribute to intervention

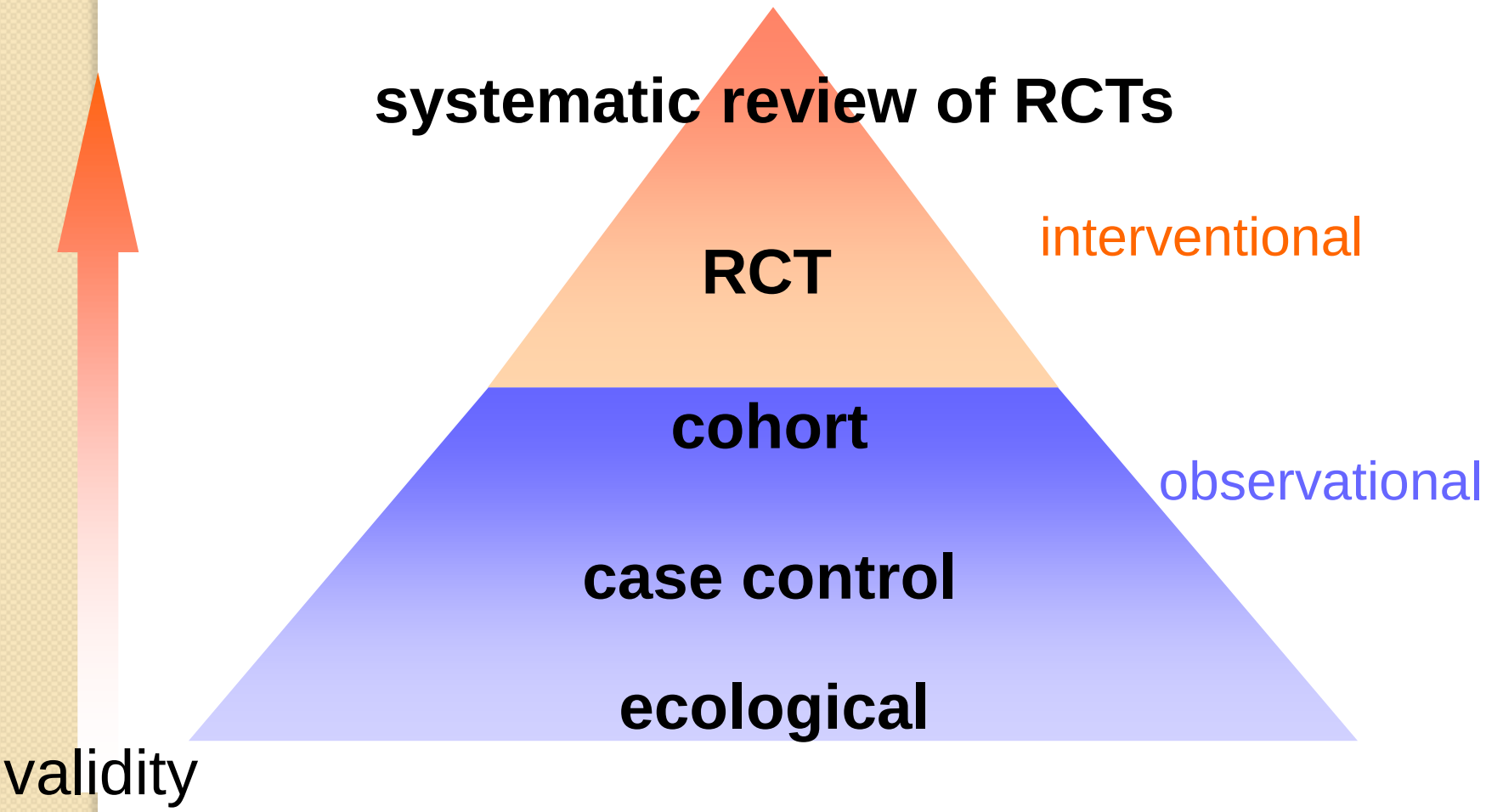
# Summary

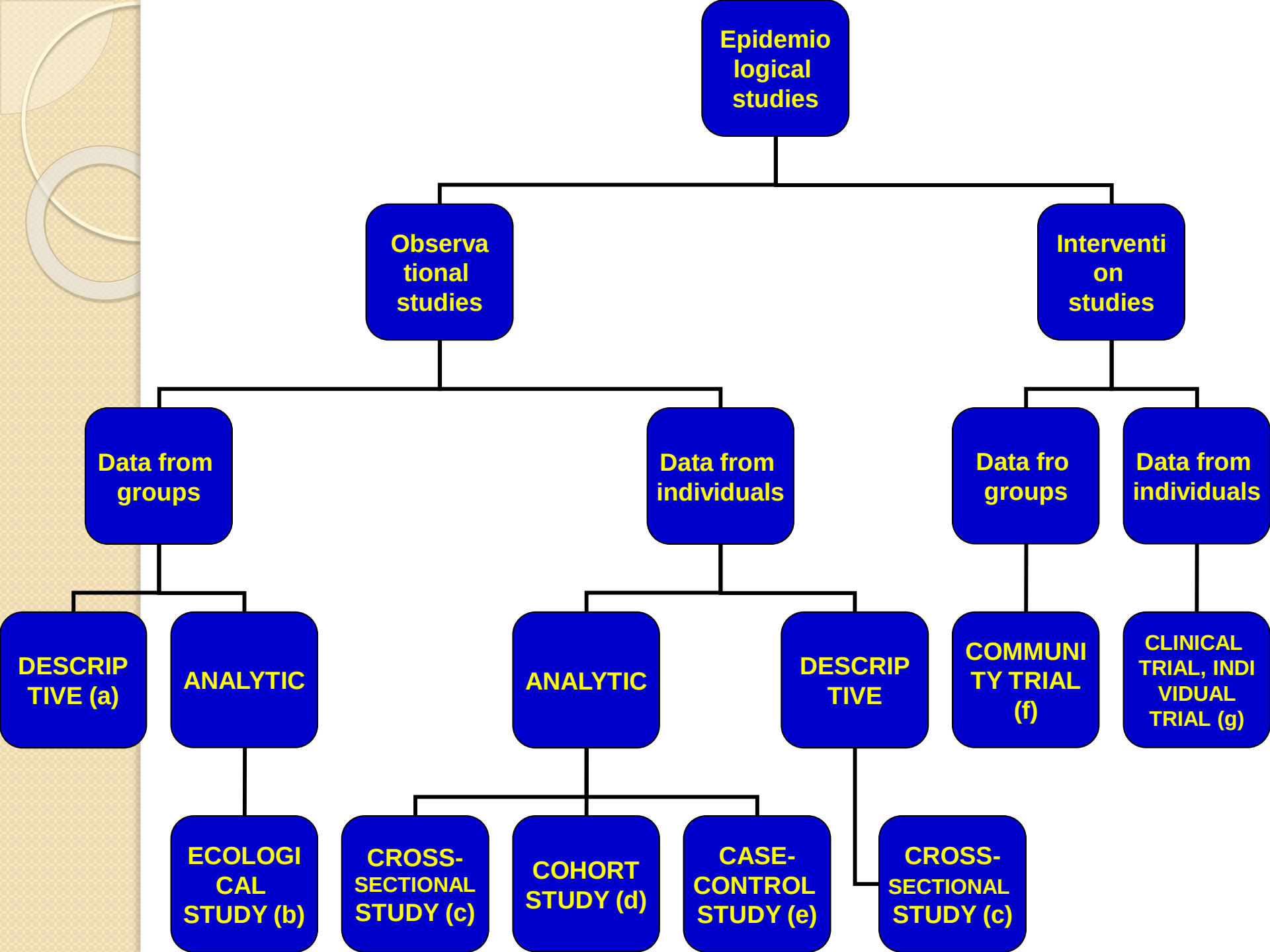
- Intervention studies are experiments
- RCTs are the gold-standard design for assessing the effectiveness of interventions
- Simple concept but many key features - need to carry out properly
- Randomisation is the most important, but others (generalisability/entry criteria, assessment, blinding, allocation concealment, analysis-ITT) also matter
- Not always applicable – PH interventions are usually more complex than a clear-cut simple experiment

# Types of comparisons in different types of studies

| Study design | Type of comparison |
|---|---|
| Ecological studies | Comparing disease frequency between populations |
| Cross-sectional studies | Comparing disease frequency between persons with and without characteristic of interest |
| Cohort studies | Comparing disease incidence between exposed and unexposed persons |
| Case-control studies | Comparing frequency of (past) exposure between cases and healthy controls |
| Interventional studies | Comparing incidence of events in persons exposed to the intervention of interest and in control group |

# hierarchy of major study designs




Epidemiological studies
Observational studies
Intervention studies
Data from groups
Data from individuals
Data fro groups
Data from individuals
DESCRIPTIVE (a)
ANALYTIC
ANALYTIC
DESCRIPTIVE
COMMUNITY TRIAL (f)
CLINICAL TRIAL, INDIVIDUAL TRIAL (g)
ECOLOGICAL STUDY (b)
CROSS-SECTIONAL STUDY (c)
COHORT STUDY (d)
CASE-CONTROL STUDY (e)
CROSS-SECTIONAL STUDY (c)

# Applications of different observational and analytical study designs

| | Ecological | Cross sectional | Case control | Cohort |
|---|---|---|---|---|
| Investigation of rare disease | ++++ | - | +++++ | - |
| Investigation of rare exposures | ++ | - | - | +++++ |
| Examining multiple outcomes | + | ++ | - | +++++ |
| Studying multiple exposures | ++ | ++ | ++++ | +++ |
| Measurement of time relationships between expo and outcome | + | - | + | +++++ |
| Direct measurement of incidence | - | - | + | +++++ |
| Investigation of long latent period | - | - | +++ | +++ |