Epidemiology in Practice – Data and Evidence

Background

Having observed the existence of a disease, epidemiology seeks to describe its properties in the population, so as to help understand

- Causes of the disease
- Who is at risk
- Strategies for prevention
- Strategies for treatment
- Future disease burden

Learning outcomes

- Be able to distinguish each type of study design by its core defining features
- To understand the major sources of data on health and illness in the UK
- To be able to describe the strengths and weaknesses of each type of study

Epidemiologic approaches

- Case report/series
- Routine data
- Cross-sectional survey

- Case-control studies
- Cohort studies

- Randomised Controlled Trials

- Systematic reviews and meta-analyses

Observational studies

Descriptive

Distribution of disease including what population or sub-groups are at risk, what geographical locations, frequency over time.

- No hypothesis. Routine data / surveys.

Analytic

Testing an hypothesized association between human exposure and adverse health effects.

– Specific hypothesis . Cases- control and cohort.

Routine data

"Data that are routinely collected and recorded in an ongoing systematic way, often for administrative or statutory purpose and without any specific research question in mind at the time of collection"

Hansell A, Aylin P. *Using routine data in health impact assessment. BMJ* 2001.

Advantages of routine data

- Relatively cheap
- Already collected and available
- Standardised collection procedures
- Relatively comprehensive – population coverage, large numbers
- Wide range of recorded items
- Available for past years
- Experience in use and interpretation

Disadvantages of routine data

- May not answer the question (no information or not enough detail)
- Incomplete ascertainment (not every case captured)
- Variable quality (e.g. missing or imprecise diagnosis fields)
- Validity may be variable (i.e. do they measure what you think they measure?)
- Disease labelling may vary over time or between geographical areas
- Coding changes may create artefactual increases or decreases in rates
- Need careful interpretation

Examples of routine data

- Health outcome data
  e.g. deaths, admissions and consultations, prescriptions, immunisations, screenings
- Exposure data
  e.g. smoking, air pollution, alcohol consumption, noise levels, pesticide use, crime statistics
- Population data
  e.g. Census population counts

Health outcome data

- Deaths
- Births
- Cancer
- Notification of infectious diseases
- Terminations
- Congenital anomalies
- Hospital episodes
- GP data
- Prescription data

Vital registration: Information Collected in E&W

Births

Date of birth
Place of birth
Name
Sex

Names of parents
Occupation of parents

Informant

Marriages

Date of marriage
Place of marriage
Names i
Occupations
Previous marital status
Ages

Names of parents
Occupation of fathers
Form of ceremony

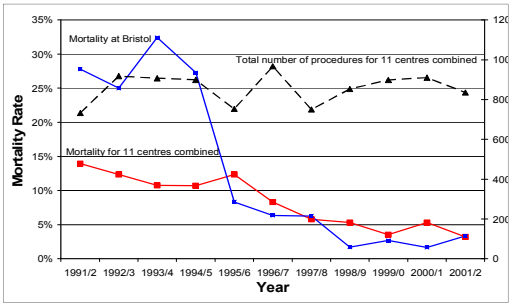
Deaths

Date of death
Place of death
Name
Sex
Occupation

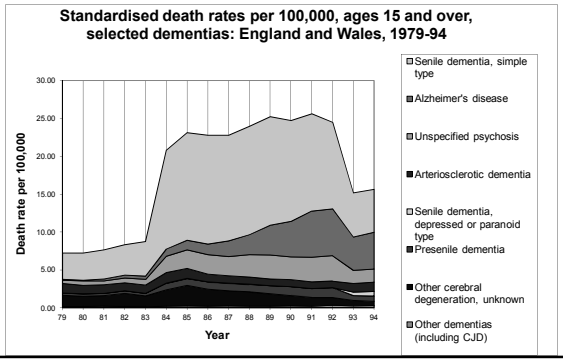
Age at death
Cause of death
(up to three causes)

Informant

Mortality rate* for and number of open operations on children aged under one year from April 1991 to April 2002 in 11 English centres; data derived from Hospital Episode Statistics (HES



Beware changes in coding!

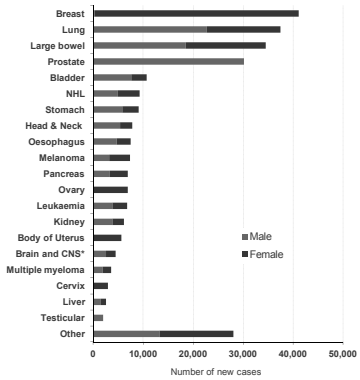


Cancer registrations

- Voluntary notification to local cancer registry
- Can be electronic or paper notification
- Also from death certificates
- Useful for both incidence and survival information
- Useful web site

  http://info.cancerresearchuk.org/cancerstats/

Most common cancers in the UK



Infectious disease notifications

- Reported by doctors
- Incidence of disease
- Includes food poisoning, meningitis, tuberculosis and plague

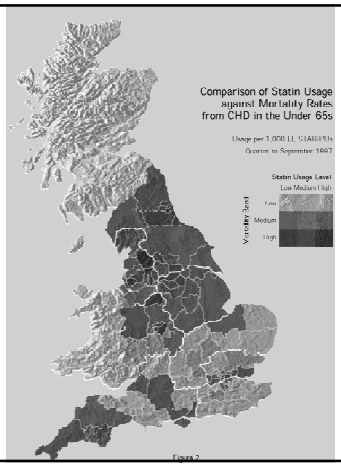
  More information on http://www.hpa.org.uk/

Notifiable diseases

Acute encephalitis
Acute poliomyelitis
Anthrax
Cholera
Diphtheria
Dysentery
Food poisoning
Leptospirosis
Malaria
Measles
Meningitis
Meningococcal septicaemia (without meningitis)
Mumps
Ophthalmia neonatorum
Paratyphoid fever
Plague
Rabies
Relapsing fever
Rubella
Scarlet fever
Smallpox
Tetanus
Tuberculosis
Typhoid fever
Typhus fever
Viral haemorrhagic fever
Viral hepatitis
Whooping cough
Yellow fever

GP data (consultations ± prescribing)

- Disease burden
- Risk factor burden
- Management of disease / risk factors
- Quality of care
- Weekly Returns Service (spotter practices) as early warning system
- Longer term collection of data enables outcomes studies



Cross-sectional surveys

- Snapshot of a population describing the distribution of factors or disease in relation to:
  - Person (age, sex, race, marital status, occupation, lifestyle)
  - Place (variation between and within countries)
  - Time (variation over time and season)

Pros and Cons

- **Quick and easy**
- Useful for health care providers to allocate resources and plan prevention
- Provide clues to aetiology, leading to hypotheses for testing in analytical studies
- Exposure and disease assessed at the same point in time, thus cannot easily distinguish whether exposure preceded disease

Examples of cross-sectional surveys

- Health Survey for England
- 2001 Census

Health Survey for England

- Series of annual surveys about the health of people in England
- First proposed in 1990 to improve information of morbidity by the (then) newly created Central Health Monitoring Unit within the Department of Health

Survey aims

- Annual data about the nation's health;
- Estimate the population with specific health conditions;
- Estimate the prevalence of key risk factors
- Examine differences between population sub-groups;
- Monitor targets in the health strategy;
- Measure the height of children at different ages.

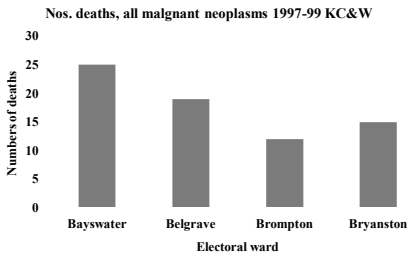
‘Core' includes

- questions on general health and psycho-social indicators
- smoking
- alcohol
- demographic and socio-economic indicators
- questions about use of health services and prescribed medicines - the focus for these may vary from year to year to suit the modular content of the survey.
- blood pressure
- measurements of height, weight and blood pressure

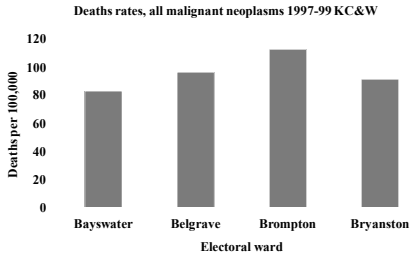
Census

- Every 10 years
- Population estimates
- Health question
- Other health indicators
- Unemployment
- Ethnicity
- Age
- Overcrowding

Why population estimates?



Why population estimates?



Epidemiologic approaches

- Case report/series
- Routine data
- Cross-sectional survey

- Case-control studies
- Cohort studies

- Randomised Controlled Trials

- Systematic reviews and meta-analyses

Clinical trials

Unique Water: a miracle cure?

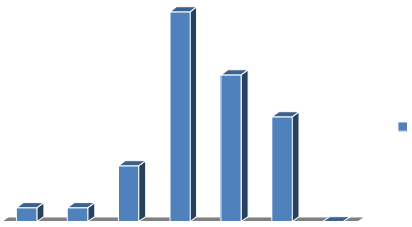
Importance of good trials

- 1949 Harvard scientists suggested that an synthetic hormone, diethylstilboestrol (DES) might prevent miscarriage
- evidence?
  - *Case reports* of successful use
- by late 1950s up to 15% of pregnant women were given DES

Further research on DES

- 1958 Randomised controlled trial
- No effect on miscarriage
- Use of DES gradually declined

Epidemic of vaginal cancer in US



Investigation of vaginal cancers

- Case control study

	Cases	Controls
DES	7	0
no DES	1	32

DES adverse effects

- Daughters of women who took DES have higher risk of
  - Vaginal carcinoma
  - Infertility
  - Tubal pregnancy
  - Miscarriage
  - Premature delivery
- Men exposed to DES before birth have genital abnormalities
- Women who took DES are at increased risk for breast cancer

Hierarchy of studies

Mainstream use requires evidence from

- **Systematic reviews and meta-analyses**
- **Randomised Controlled Trials**

Observational studies give only limited support

- Cohort studies
- Case-control studies
- Descriptive/cross-sectional studies
- Case report/series

Clinical trials

- a planned **experiment** in humans designed to measure the effectiveness of an intervention, eg.
  - a new drug
  - a surgical procedure
  - a vaccine
  - complementary therapy

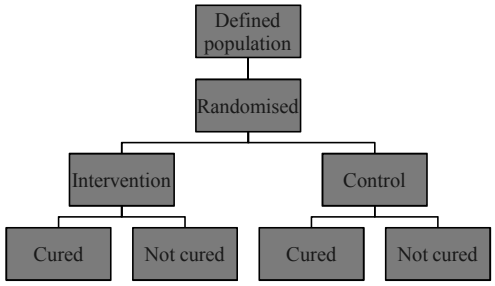
Different from other epidemiological designs

- Most epidemiological studies (surveys, cross sectional, cohort, case control, ecological) are **observational**
- Trials are **experimental**

Phases of clinical trials for drug development

- **Phase I**
  - test the safety of a new treatment
  - small number of people, usually healthy volunteers
- **Phase II**
  - Test to see whether the treatment is effective (surrogates)
  - Continue to look at safety
  - a few hundred people usually with the condition
- **Phase III**
  - Compare the new treatment with the current or placebo (hard)
  - Continue to monitor side effects
  - Several thousand patients
- **Phase IV**
  - After drug has been marketed
  - Measure effect in various populations, rare side effects

Overview of clinical trial design



Core features of a clinical trial

- Clear entry criteria
- Control group
- Randomisation
- Blinding
- Clear endpoint criteria

Why randomise?

- To remove **bias** in treatment allocation
- Otherwise the investigator may chose different patients for each group.
- BGC vaccine for TB in children
  - deaths from TB were five times higher in the control group than the vaccinated children
  - doctors offered new vaccine to children with “cooperative” parents
  - These parents were more educated, health conscious
  - Their children had lower mortality from TB regardless of the vaccination

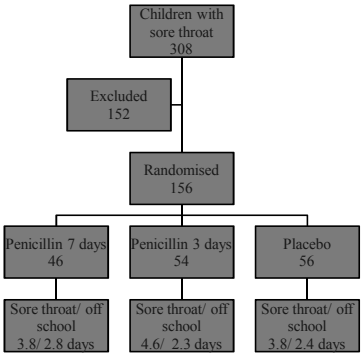
Blinding

- Single blind
  - The patient does not know whether they are getting the new treatment or not
- Double blind
  - neither the patient nor the doctor knows which treatment they are getting

Clear and appropraite endpoints

- Death from any cause
- Death from the target condition
- Complete response / disease-free survival
- Partial response
- Clinical response / time to progression

Example 1: RCT of penicillin in children with sore throat



Summary of findings

- Penicillin V does not reduce the duration of symptoms or the use of analgesics
- Penicillin V does not affect school attendance

Example 2: Salk Polio vaccine, 1954

- RCT
- Hundreds of thousands of children
  - Salk vaccine
  - control

Results of Salk Polio trial

Group	Number	Cases of polio	Rate per 100,000
Vaccinated	200745	33	16
Control	210229	115	57

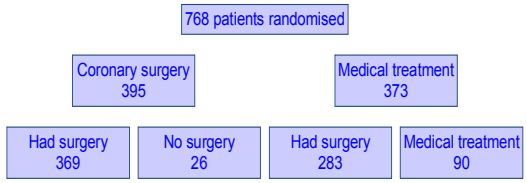
Example 3:
European Coronary Surgery Trial

Comparison of treatments for angina

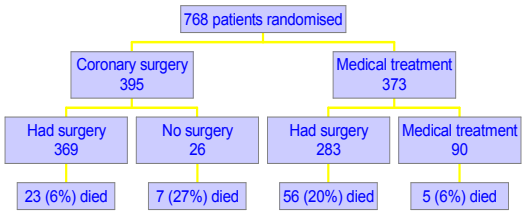
768 patients randomised

Coronary surgery 395 | Medical treatment 373

European Coronary Surgery Trial



European Coronary Surgery Trial



Options for protocol deviants

1. Exclude protocol deviants
2. Analyse the data as four groups
3. Analyse according to treatment actually received
4. Analyse according to treatment originally allocated

European Coronary Surgery Trial

768 patients randomised

Coronary surgery 395 | Medical treatment 373

Total deaths 30 (7.6%) | Total deaths 61 (16.3%)

Ethics and consent

- Regulation aims to protect patients
- All participants in a trial must provide informed consent, and be free to withdraw at any time without affecting their care
- All clinical trials have to be
  - Registered
  - reviewed by an independent scientific committee
  - approved by a Research Ethics Committee
  - adhere to government and international guidelines.
- Independent data monitoring committee
  - researchers check progress during the trial
  - Unblind the results to see if there is any major difference in outcome
  - If there is a large difference they have the power to stop the trial.

bbc.co.uk

BBC NEWS

Six taken ill after drug trials

Six men remain in intensive care after being taken ill during a clinical drugs trial in north-west London.

The healthy volunteers were testing an anti-inflammatory drug at a research unit based at Northwick Park Hospital when they suffered a reaction.

Relatives are with the patients, who suffered multiple organ failure. Two men are said to be critically ill.

An investigation has begun at the unit, run by Parexel, which said it followed recommended guidelines in its trial.

The men were being paid to take part in the early stages of a trial for the drug to treat

Epidemiologic approaches

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- Systematic reviews and meta-analyses

Systematic Reviews and Meta-analyses

Learning outcomes

- Understand the need for conducting systematic reviews and meta-analyses.
- Appreciate the potential biases and limitations of systematic reviews and meta-analyses.
- Able to interpret the findings presented in published systematic reviews and meta-analyses.
- Able to critically appraise published systematic reviews and meta-analysis.

Limitations of a single study

- The number of patients included in a single study or trial is often insufficient
- Biased or false –ve / false +ve results are common.
- The studies often only look at a subset of the population, making the results difficult to generalise.

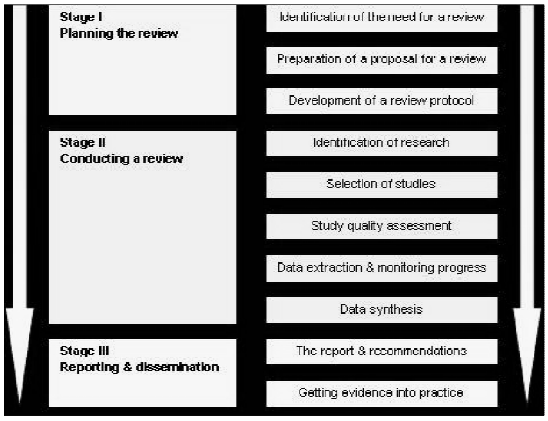
Systematic Review

'A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review.'

Cochrane collection glossary (www.cochrane.org)

Advantages of systematic review

- Large amounts of information from a range of sources/languages), providing an **overview of evidence**.
- Explicit methods **limit bias**; conclusions are thus more **reliable and accurate**.
- Results of different studies are compared to establish **generalisability** and **consistency**.
- Inconsistencies can be identified and **new hypotheses generated** about subgroups.
- Quantitative systematic reviews (meta-analyses) **increase the precision** of the overall result.



Stage I - Planning the review

Need to specify the question to be addressed, usually framed around:

- The population
- The exposure/intervention
- The outcomes
- The study designs

Stage II - Identification of research

- Clearly defined search criteria :
  MeSH (Medical Subject headings), free text words and Boolean operators
- Systematic search of published medical literature including electronic databases
- Search other sources
  - Reference lists/citation searches
  - Conference proceedings/grey literature
  - Contacting established researchers in the field to identify unpublished studies.

Stage II - Selection of studies

Eligibility/Inclusion criteria may be based on*:*

- Study design
- Year of study
- Publication language
- Sample-size/precision
- Specific exposure/intervention
- Specific outcome
- Completeness of information

Stage II - Study quality assessment

- Study quality should be assessed according to recognized e.g. Cochrane Handbook for Systematic Reviews of Interventions
- Quality criteria should assess for bias in study design:
  - Selection bias
  - Measurement bias
  - Attrition bias/loss to follow-up
- Study design quality should be assessed before study results known, and should be assessed independently by more than one assessor.

Stage II - Study quality assessment

Jadad score is widely used :

- Randomized?
- Randomization adequately described?
- Double blinded?
- Blindness adequately described?
- Description of withdrawals?

Stage III - Reporting and dissemination

- Study details should be provided , including:
  - the populations
  - the interventions/exposure
  - the outcomes
  - the study design
- Findings should be summarised.

Reviewing a systematic review

1. Clear, unambiguous and predefined question? (Populations, interventions/exposures, outcomes and study designs)
2. Comprehensive search for relevant literature? (Grey literature; time frame; appropriate inclusion/exclusions; languages; duplicate & independent assessment of literature)?
3. Methodological quality of each study assessed? (Quality as and inclusion criterion quality measures appropriate, studies weighted according to quality)?
4. Heterogeneity and bias explored? (Population, interventions, exposures, outcomes and study designs, publication bias)?
5. How credible is the evidence?
   Strengths and weaknesses of evidence? Evidence from high quality studies? Impact on clinical practice?

Meta-analysis

'The use of statistical techniques in a systematic review to integrate the results of included studies'.

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Advantages of meta-analyses

- Meta-analysis techniques combine the published estimates of effect from each study to generate a **pooled overall risk estimate**.
- Can include **more subjects** than any single constituent study, and produce a more **reliable and precise** estimate of effect
- Can **explore differences** (heterogeneity) between published studies.
- Can identify whether **publication bias** is occurring.

BUT

- If the studies are **too heterogeneous**, it may be inappropriate, even misleading to statistically pool the results from separate studies!

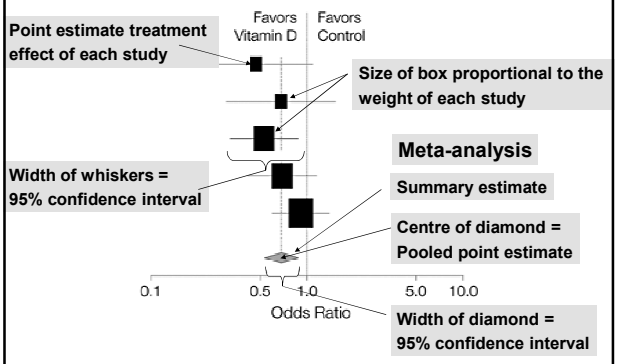
What does a meta-analysis involve?

- Effect estimates are abstracted (or calculated) from the selected studies
- These individual study effect estimates are pooled to produce a weighted average effect across all studies.
- Studies are weighted according to a measure of its importance.
  - Most weight to informative studies (often large studies with precise effect estimates)
  - Least weight to less informative studies (often smaller studies with imprecise effect estimates).

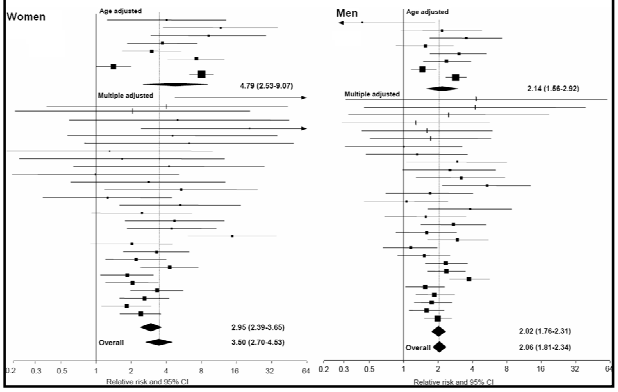
Presenting the results

- A Forest plot is a common way of presenting the results from a meta-analysis
- A Forest plot is a graphical representation of the results from each study included in a meta-analysis, together with the combined meta-analysis result.
- The overall estimate from the meta-analysis is usually shown at the bottom, as a diamond.

Presenting the results - Forest plots



Reporting – Forest plot

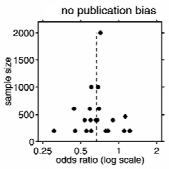


Publication Bias

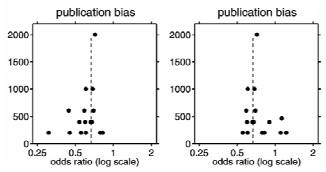
- Failure to include all relevant data in a meta-analysis may mean the effect of an intervention/exposure is over (or under) estimated.
- **Publication bias** is caused when only a subset of the relevant data is available.
- Null or non significant findings (esp. in small studies) are less likely to be reported/published than statistically significant findings.

Publication bias - Funnel Plot

A funnel plot which is symmetric about the mean effect and shaped like an upside down funnel indicates no publication bias.



A plot with the lower right or left hand corner of the plot missing indicates that publication bias is present.



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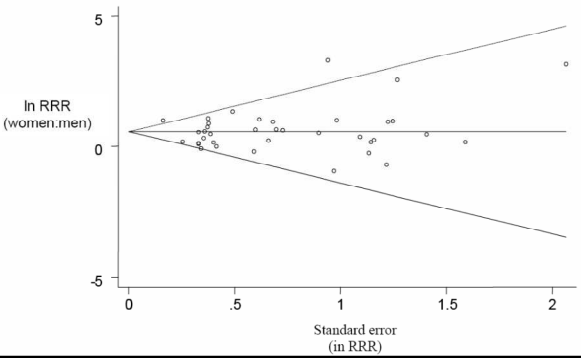


Heterogeneity

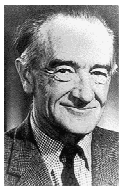
- Studies differ with respect to:
  - Populations
  - Interventions/exposure
  - Outcomes
  - Study design
- Even where these factors are homogeneous, heterogeneity may still exist because of :
  - Clinical differences
  - Methodological differences
  - Unknown study characteristics

Reviewing a meta-analysis

Similar points to reviewing systematic reviews…

1. How sensitive were the results to the way the review was carried out?
2. Was heterogeneity explored?
3. Was publication bias an issue?
4. Was it appropriate to pool the studies?
5. Did different sub groups of studies give similar results?

The Cochrane Collaboration



- Founded in 1993 and named after the British epidemiologist, Archie Cochrane.
- The Cochrane Collaboration produces and disseminates systematic reviews of healthcare interventions.
- The major product of the Collaboration is the **Cochrane Database of Systematic Reviews** which is published quarterly as part of the Cochrane Library.
- Deals mainly with clinical controlled trails of healthcare interventions.

www.cochrane.org

THE COCHRANE COLLABORATION®

Conclusions

- Single studies rarely provide a conclusive, universal answer to a question.
- Systematic reviews can provide an invaluable overview of evidence on a particular topic.
- Meta-analyses can provide:
  - A single, more precise, estimate of intervention/exposure effect.
  - A greater understanding of similarities/differences among studies.
  - An assessment of likely publication bias.
- Inconsistencies in results across studies can be identified and new hypotheses generated about particular subgroups.
- Systematic reviews/meta-analyses can provide a evidence-base for clinical decisions.