Etiology / Harm / Causation
DEN1014 Clinical Epidemiology

How can one prove that something is safe or harmful?

Some issues in Dentistry

Bacterial endocarditis and A.b. Prophylaxis

INR significant vs non-significant bleeding?

Effect of smoking on ....

Amalgam health risk?

Bisphenol-A from sealants health risk?

Bisphosphonates and bone necrosis risk?

Relationship between periodontitis and ....

"Infection-control" – use of masks/ gloves – cling film – more cling film – single use XXX ...

Asking Focused Questions
Finding the Evidence
Levels of Evidence
Levels of Evidence #2
Searching Exercise
Critical Appraisal
Making a Decision
Evaluating Performance
Designing Research

Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009)

What are we to do when the irresistible force of the need to offer clinical advice meets with the immovable object of flawed evidence? All we can do is our best: give the advice, but alert the advisees to the flaws in the evidence on which it is based.

The CEBM 'Levels of Evidence' document sets out one approach to systematising this process for different question types.

(For definitions of terms used see our glossary)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"¡)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" " " reference standards; or CDR" tested within one clinical	Prospective cohort study with good follow -up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and

Other Formats

This Levels of Evidence page is available for download in a range of other formats for your convenience. Please click on the appropriate links below.

- Word (.doc)
- Office 2007 (.docx)
- PDF (.pdf)
- Real Text Format (.rtf)

- Spanish (abridged) extract from Sociedad Mexicana de Ortopedia Pediatrica

Three relevant terms

- Association
- Risk
- Causation

Association

- Two variables appear to be related by a mathematical relationship. A change of one appears to be related to the change in the other.
- Necessary for a causal relationship to exist, but association alone does not prove that a causal relationship exists.
- E.g. surface discolouration and wear of composite resins are often associated, but there is no causal relationship.

Risk

- The likelihood that a specified outcome will develop *in a defined time period*.
- E.g. risk of implant fracture within five or ten years.
- A **risk factor** is an attribute (intrinsic characteristic) or exposure (external environment) that is positively or negatively associated with the occurrence of a specified outcome.
  - Small diameter implant in the posterior mand.

Causation

- Combination of necessary and sufficient factors, the presence of which, alone or in combination, at some time inevitably result in an incidence of interest.
- A **necessary factor/cause** is a risk factor that must be, or have been, present for a specified outcome to occur.
- A **sufficient factor/cause** is the minimal or combination of risk factors that inevitably results in a specified outcome

Causation

Henle-Koch Postulates (1877)

Four postulates applied to establish the etiology of anthrax and tuberculosis

General guidelines to identify pathogens

Today only of historical interest

Causation

- Henle-Koch Postulates (1877)
  - Germ theory, today archaic
- Hill-Evans Postulates
  - Mill's Eliminative Methods of Induction (System of Logic, 1843)
  - Hill's Criteria of Causation (1965)

Bradford Hill A. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300.

Tests for causation

1. Is there evidence from true experiments in humans?
2. Is the association strong?
3. Is the association consistent from study to study?
4. Is the temporal relation appropriate (did the postulated cause precede the postulated effect)?
5. Is there a dose-response gradient (does more of the postulated effect follow more of the postulated cause)?
6. Does the association make epidemiological sense?
7. Does the association make biological sense?
8. Is the association specific?
9. Is the association analogous to a previously proved causal association?

Causation

- Henle-Koch Postulates (1877)
  - Germ theory, today archaic
- Hill-Evans Postulates
  - Mill's Eliminative Methods of Induction (System of Logic, 1843)
  - Hill's Criteria of Causation (1965)
  - Evan's Postulates (1976)

Evans AS. Causation and disease: the Henle-Koch postulates revisited". Yale J Biol Med 1976; 49 : 175–95.

Evans AS. Causation and disease: the Henle-Koch postulates revisited". Yale J Biol Med 1976;49: 175-95.

a. Prevalence of the disease should be significantly higher in those exposed to the risk factor than those not.

b. Exposure to the risk factor should be more frequent among those with the disease than those without.

c. In prospective studies, the incidence of the disease should be higher in those exposed to the risk factor than those not.

d. The disease should follow exposure to the risk factor with a normal or log-normal distribution of incubation periods.

e. A spectrum of host responses along a logical biological gradient from mild to severe should follow exposure to the risk factor.

Evans AS. Causation and disease: the Henle-Koch postulates revisited". Yale J Biol Med 1976; 49 : 175-95.

f. A measurable host response should follow exposure to the risk factor in those lacking this response before exposure or should increase in those with this response before exposure. This response should be infrequent in those not exposed to the risk factor.

g. In experiments, the disease should occur more frequently in those exposed to the risk factor than in controls not exposed.

h. Reduction or elimination of the risk factor should reduce the risk of the disease.

i. Modifying or preventing the host response should decrease or eliminate the disease.

j. All findings should make biological and epidemiological sense.

Etiology - Harm - Causation

- Evidence levels: Randomised clinical trial > cohort/ clinical trial > case -control > cross-sectional > single case
- Clearly identified comparison group for those at risk for, or having, the outcome of interest
- Observers of outcomes masked to exposures
- Observers of exposures masked to outcomes for case-control studies and observers masked to exposure for all other study designs
- A statistical analysis consistent with the study design.

Cross-Sectional Survey

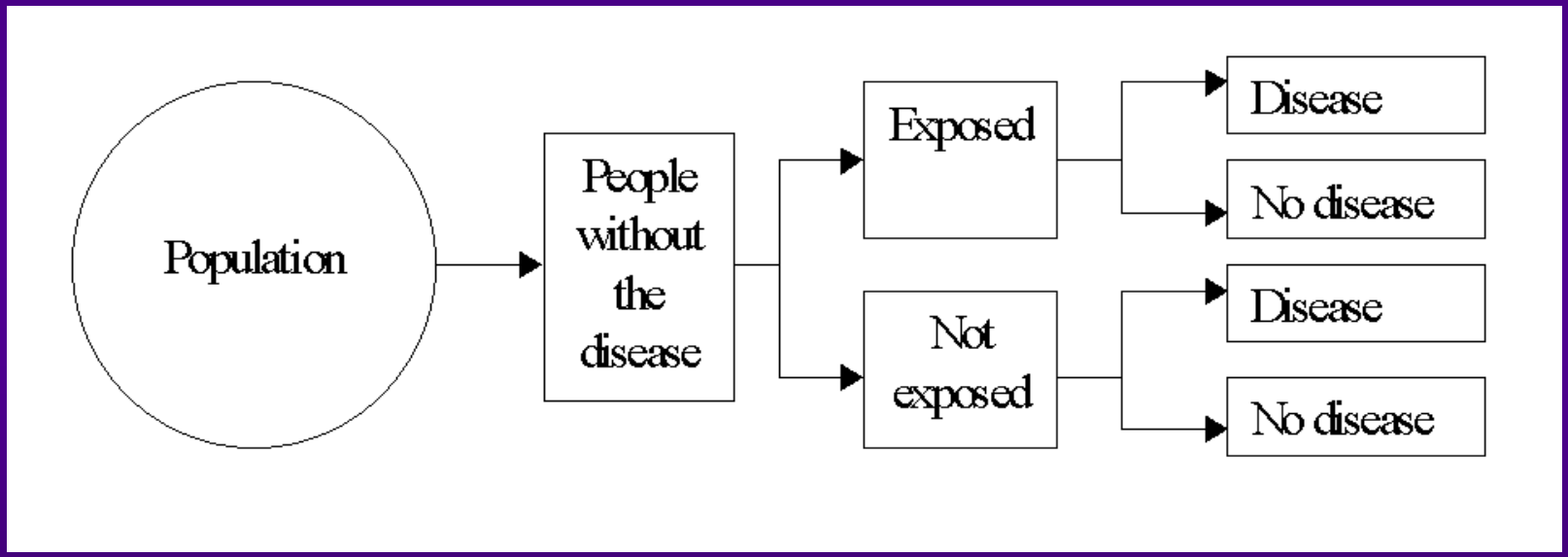
Advantages

1. Cheap and simple
2. Ethically safe

Disadvantages

1. Establishes association at most, not causality
2. Recall bias susceptibility
3. Confounders may be unequally distributed
4. Group sizes may be unequal

Cohort Study



Cohort Study

Advantages:

1. Ethically safe
2. Individuals can be matched
3. Can establish timing and directionality of events
4. Eligibility criteria and outcome assessments can be standardised
5. Administratively easier and cheaper than RCT

Disadvantages:

1. Controls may be difficult to identify
2. Exposure may be linked to a hidden confounder
3. Blinding is difficult
4. Randomisation not present
5. For rare disease, large sample sizes or long follow-up necessary

Questions to ask:

- How were subjects selected for the cohort?
- How were subjects selected for the comparison or control group?
- Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the design or analysis?
- Was the measurement of outcomes unbiased (ie blinded and comparable across groups)?
- Was follow-up long enough for outcomes to occur?
- Was follow-up complete and were there exclusions from the analysis?

Characteristics of a poor cohort study:

Fail to :

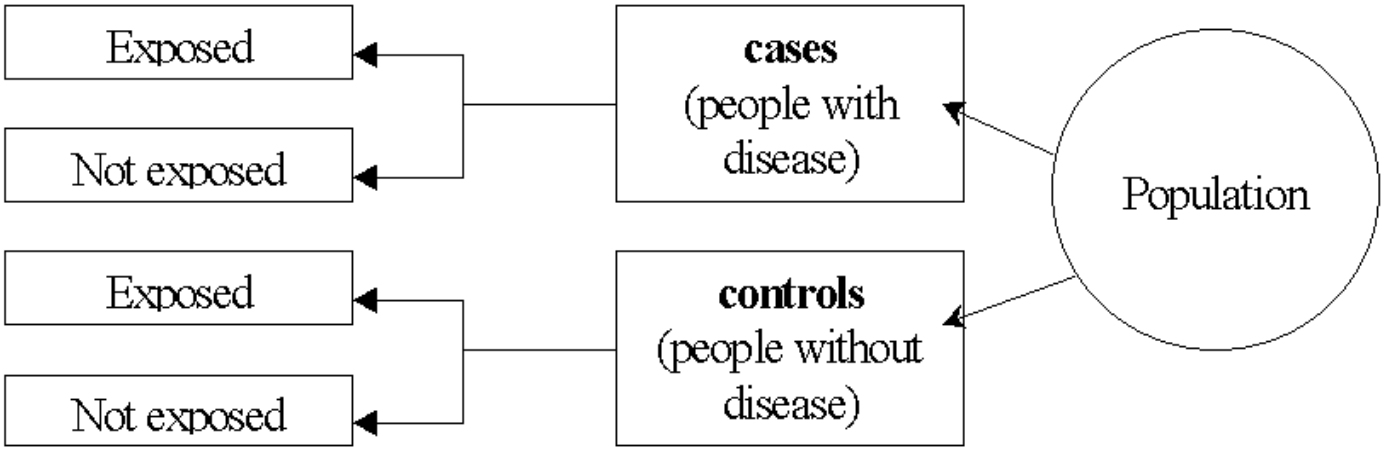
clearly define comparison groups and/or

measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or

identify or appropriately control known confounders and/or

carry out a sufficiently long and complete follow-up of patients.

Case-Control Study



Case-Control Study

Advantages:

1. Quick and cheap
2. Only feasible method for very rare clinical situations or those with long lag between exposure and outcome
3. Fewer individuals needed than cross-sectional studies

Disadvantages:

1. Rely on recall or records to determine exposure status
2. Confounders
3. selection of control groups is difficult
4. Potential bias: recall, selection

Questions to ask:

- How were cases defined and selected?
- How were controls defined and selected?
- Does the study adequately control for demographic characteristics and important potential confounders in the design or analysis?
- Was measurement of exposure to the factor of interest (eg the new intervention) adequate and kept blinded to case/control status?
- Were all selected subjects included in the analysis?

Characteristics of a poor case-control study:

Fail to:

- clearly define comparison groups
- and/or fail to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls
- and/or fail to identify or appropriately control known confounders.