From Clinical Observations to Experimental Research

Hierarchy of Study Designs

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Hierarchy of study designs

• Descriptive studies
  • Case reports, and case series
  • Reported data, and Prevalence surveys

• Analytic studies
  – Observational
    • Cross-sectional
    • Ecologic studies
    • Case control studies
    • Cohort studies
  – Experimental studies
    • Uncontrolled trials
    • Randomized or quasi-randomized controlled trials
      – Individual level
      – Field trials - community or group level
The starting point – an Observation

• Usually a clinical observation
  – An unusual case (young woman with PE)
  – An unusual cluster (3 homosexual men with PCP)
  – An unusual complication (ICU admissions for C Dif)

• Or, an observation based on reported data
  – Temporal trend (Increase in Lung cancer rates)
  – Geographic clustering (MS, gastric Ca)
Case Reports

• Report of a single occurrence of new disease or unusual occurrence of a known disease
  – Pulmonary embolus in young woman on oral contraceptives
  – Myocardial infarction in a child

• Strengths –
  – Rapid and cheap
  – Useful to alert community to a new disease
  – Particularly if others are seeing the same thing.

• Weaknesses –
  – Rare events do happen - Someone always wins the lottery
  – Clinicians have to recognize that the problem seen is unusual. Requires genuine expertise
Case series

• This means 3 or more of the same condition
  – Unusual events - as for case reports
  – Generally adds a little more than case reports
  – More cases equals potentially more weight

• But, rare events can also happen together
  – 3 cases of Angiosarcoma in workers from a PVC factory
  – Lightning strikes the same person twice
  – Three people on same street win lottery
  – All have occurred. Was one NOT due to chance?
Case series – example
Extensively drug-resistant tuberculosis as a cause of death in patients with TB and HIV in rural South Africa

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Laloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

• Among 475 patients with culture-confirmed TB:
  – 39% (185 patients) MDR-TB
  – 6% (30 patients) XDR-TB.

• Of XDR-TB:
  – 45% had been previously treated for TB ;
  – 67% had a recent hospital admission.
  – 100% of tested for HIV were co-infected.
  – 98% died, with median survival of 16 days
Large Case Series

• Description of a large number of patients with a new disease, or receiving a new treatment or new operation.

• Advantages – Comprehensive - Includes all cases

• Disadvantages – No controls or comparison population
  – Implicit comparison with standard, or previous therapy
  – Historical controls or concurrent non-randomized controls

• Thus better results can be because:
  – The new treatment IS better,

• BUT could be,
  – Better selection of patients
  – Other improvements in care, or better care at specialized centre
After the case report/case series. Need to review and understand disease

1. Case definition
   - Who gets it, clinical features, outcomes?

2. What appears to be the biology?
   - Apparent latency
   - Manifestations - what organs affected
   - Pathogenesis - probable or known

3. Review the literature
   - This is often forgotten, or under-utilized
   - But is essential to avoid mistakes and wasting time
Population characteristics – who gets the disease?

Figure 7–12. Incidence rates of mongolism by maternal age at birth from selected studies, 1923–1964

Understanding the disease - latency and duration

• Latency refers to interval between exposure and disease.
• Plausible that exposure leads to disease if interval from exposure to disease fits with known latency.
Latency and clinical acumen

• The shorter the latency the easier to link exposure and disease
  – Immediate – eg Grain workers and asthma
  – <24 hours “must have been the egg salad”
  – < 1 week – “I think I caught this from Fred”
  – If longer it gets harder. “So many exposures, so much time, and so little memory” (recall)
    • Asbestos and mesothelioma
    • Smoking and most diseases
Distribution of incubation in common-source outbreak from gravy contaminated with *Clostridium perfringens*. 
Reported Data

• Reported data commonly used
  – TB, HIV, Cancers
  – Useful if this is COMPLETE

• Useful to:
  – Define incidence/prevalence
  – Identify geographic or temporal differences
  – Describe clinical characteristics
  – Describe outcomes.

• Implicit comparison with general population
  – Risk factors can be identified.
Temporal trends may indicate clues to causal exposure
Coal use and TB in USA: 1953 – 2003

Coal use (▲) and TB incidence (◊).

Coal use (▲) and TB incidence (◊).
Temporal trends may indicate clues to causal exposure
Coal use and TB in China: 1978 - 2004

Total coal consumption (exajoules) vs. Years

TB notification rate (per 100,000 ha.) vs. Years

Total coal combustion (—) Notified cases of TB (—).
Ecologic Studies

Advantages

• Usually very easy and quick studies
• Take advantage of already gathered data
  – Exposures
  – Diseases

Disadvantages

• Relationship may be due to completely unmeasured factors
• VERY substantial potential for confounding
Ecologic study – Geographic distribution may indicate clues to exposures: Skin test sensitivity to coccidiomycosis and place of residence

Figure 7-9. Percent reactors to coccidioidin skin test among white men and women, 17-21 years of age, by county of residence, United States, 1945-1951

Source: Edwards and Palmer (11).
Directionality in research - Backward

• Retrospective: Start with a persons with disease and ‘look backward’ in time to ascertain exposures.

• Advantages: Biggest is convenience – do not have to wait a long time, because disease HAS happened.
  – Makes these studies much quicker to complete, and much cheaper.
Observational studies – You gather the data:

- Prevalence surveys – Easy to design, Moderately time consuming and expensive to conduct
- Case-control – hard to design, Quick and easy to conduct
- Cohort studies – moderately hard to design. Very time-consuming and expensive to conduct
Directionality in research - Forward

• Prospective: Start with a population and observe them ‘going forward’ in time. Exposures are measured first, and health events are measured afterward, as they occur.

• Advantages: Biggest is accuracy of exposure
  – Also certainty that exposure is followed by disease, not simply coincidental
Retrospective designs: Prevalence or cross-sectional studies

General approach:
- Pick a disease (can pick several)
- Identify the possible exposures (can pick several)
- Pick a population (one time survey)
- Data gathering:
  - Measure who has the disease
  - Measure who has the exposure.
- Analysis: Association of disease presence with exposure presence (Prevalence odds ratio)
Advantages

• Good for common/chronic diseases
• Also good for fairly common exposures
• Allows one to measure multiple disease or conditions and multiple exposures

Disadvantages

• Measurement of exposure often difficult
  – Recall problems if long latency
  – May change over time (Alcohol, smoking, blood pressure)
• Can not distinguish cause and effect
  – (Tobacco Industry defense)
Tuberculin (or IGRA) Surveys
A special type of cross-sectional survey

• Once TST or IGRA convert to positive with TB infection – they remain positive lifelong
• Cross-sectional survey – detects all with positive tests – from recent or remote
• From prevalence of positive test at a given age – can calculate average annual risk of TB infection.
• Can compare prevalence in different populations
• If different ages, or different exposure periods can estimate trends in infection
Does Size matter? Relationship of patient’s diagnosis to size of TST

(from Al-Zahrani et al AJRCCM, 2000)
University students in Brazil
(All BCG vaccinated in infancy)
Silva et al. IJTLD2000; 4:420-426

![Bar chart showing the percentage of reaction by years of training and study level.]

- **Engineering Students**
  - Early 0-2: 4%
  - Intermediate 3-4: 6%
  - Senior 5-6: 4%

- **Medical Students**
  - Early 0-2: 4%
  - Intermediate 3-4: 8%
  - Senior 5-6: 16%

Average ARI:
- Preclinical: 0.2%
- Clinical: 2.9%

Incidence of TB in Brazil: 75/100 000
Example of Kaplan-Meier analysis: General Hospital Ventilation and time to TST conversion
Retrospective Analytic Studies: Case Control

General design

• Identify Cases - patients with disease
• Identify Controls - without disease
• Measure exposures in both
• Analysis - is exposure more likely (odds > 1) in cases than controls
Case Control study – example
TB outbreak in Kangiqsualuujuaq

Factors associated with acquisition of TB infection during the outbreak.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Newly Infected, N=88 N(%)</th>
<th>Uninfected, N=67 N(%)</th>
<th>Crude OR (95CI)</th>
<th>Adjusted OR (95CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 15</td>
<td>24 (27)</td>
<td>34 (51)</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Age 15 - 29 y.o.</td>
<td>41 (47)</td>
<td>26 (39)</td>
<td>3.8 (2.1 - 6.9)</td>
<td>4.2 (1.7 - 10.3)</td>
</tr>
<tr>
<td>Age ≥ 30 y.o.</td>
<td>23 (26)</td>
<td>7 (10)</td>
<td>4.2 (1.5 - 12)</td>
<td>5.0 (0.8 - 30)</td>
</tr>
<tr>
<td>Visited a gathering house</td>
<td>47 (53)</td>
<td>16 (24)</td>
<td>3.7 (1.6 - 8.1)</td>
<td>3.6 (1.3 - 9.9)</td>
</tr>
<tr>
<td>Lived with smear-positive person**</td>
<td>20 (23)</td>
<td>1 (1)</td>
<td>19 (3.3 - 113)</td>
<td>20 (4.0 - 100)</td>
</tr>
</tbody>
</table>
Case Control Studies

Advantages
• Relatively cheap and quick
• Particularly useful for studying rare conditions
  – Or conditions with long latency

Disadvantages
• Controls, Controls, Controls
  – Very difficult to select proper controls
  – This is the source of most problems in case control studies
  – And is why they are generally considered weak evidence.
• Difficulties of retrospective exposure assessment
  – particularly if long latency
Analytic Studies – Cohort studies

General design

• Start with population free of disease (of interest)
• Measure of interest
• Follow them for a period of time
• Measure occurrence of disease
• Analysis – occurrence of disease in persons who had/did not have exposure of interest
Average Annual Incidence of Tuberculosis Among Navy Recruits
By History of Household Contact

Cohort Studies

Advantages
- Can measure many exposures
- Can measure many diseases
- Temporal relationship clearer (cause before disease)

Disadvantages
- Long and expensive (often very $$$)
- Good for common diseases (some cancers, cardiovascular)
- Inefficient for rare diseases or with long latency
- Also what if you fail to measure key determinants
  - (Solution = freezer)
Experimental Studies:

Uncontrolled

- No control or comparison group
- Phase 1 or Phase 2 drug trials
Experimental Studies:

Controlled Trials

• Non-randomized – allocation to different not done randomly, but rather purposely
• Quasi-randomized – allocation to intervention groups not randomly, but using schemes such as: date of birth, days of week, hospital records
• Randomized – allocation is random so all participants have equal chance of getting each intervention
Experimental Studies – Randomized Trials

General Design

• Pick an intervention – usually a form of treatment
  – You can only pick one
• Find a group of patients that agree to participate
  – Have to be representative of condition
• Give the new treatment to some
  – Some get the old (or no) treatment
  – Do this randomly
• Follow all to see outcomes
Randomized Trials

Intensified regimen containing RIF and Mfx for TB meningitis: an open-label, randomised controlled phase 2 trial

Rovina Ruslami*, A Rizal Ganiem*, Sofiati Dian, Lika Apriani, Tri Hanggono Achmad, Andre J van der Ven, George Borm, Rob E Aarnoutse, Reinout van Crevel

- Open-label, phase 2 trial. Factorial design
- Patients aged >14 with TB meningitis
  - All received INH & PZA & Steroids
- Randomly assigned for 14 days – by computer-generated schedule:
  - RIF: 450 mg vs 600 mg, intravenously, and
  - Mfx 400 mg, or Mfx 800 mg, or EMB 750 mg daily.
- 14 days of treatment all patients, then routine treatment.
- Endpoints: PK analyses (blood and CSF) adverse events attributable to tuberculosis treatment, and survival.
Randomized Trials

Advantages
• Best way to evaluate an intervention
• Best control of bias and confounding

Disadvantages
• Not easy or feasible for all interventions
• Not for studies of risk factors or natural history
• Substantial refusal or drop-out rates can restrict generalizability
• Population selected may not be representative
  – Younger adults with only one condition
  – Often exclude pregnant woman, kids, elderly!
Experimental Community or Field Trials

General Design

• Pick an intervention to be applied at a community level
  – Fluoride in water, public education, vaccination
• Find several communities or population groups
• Apply intervention to some and not others
  – Randomly again
• Measure outcomes at population or group level
Cluster randomized Trials – example
Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial
Betina Durovni, Valeria Saraceni, Lawrence H Moulton, Antonio G Pacheco, Solange C Cavalcante, Bonnie S King, Silvia Cohn, Anne Efron, Richard E Chaisson, Jonathan E Golub

- 29 HIV clinics in Rio de Janeiro.
- Staff trained in TB screening, TST and INH.
- Clinics randomly allocated when began the intervention period. 2 clinics started every 2 months starting from Sept 2005, until Aug 2009
- Outcome: TB incidence +/- death
Community or Field Trials

Advantages
• Only way to study some interventions
• May offer better assessment of likely impact of these interventions

Disadvantages
• All the same problems as ecologic studies
• Also some important ethical issues (eg., fluoride)
Thanks