Design of Observational and Experimental Clinical Studies

Skamania ICSSC 2007

Kenneth F. Schulz, PhD
Epidemiology:
The study of epidemics and epidemic diseases.

Stedman’s Medical Dictionary
Epidemiology:
The science of making the obvious obscure.

Epidemiologist
Epidemiology:

The worst-taught course in medical school.

Anonymous Med Student
Epidemiology: The study of skin diseases.

North Carolina Native
Epidemiology

- More than statistics; biostatistics; medical science - a specific research methodology
- “Methods” conjures up what images?
- Has a bad rap - really fun and exhilarating
- Part of the interest is that sometimes it runs counter to intuition
Epidemiology of AIDS Before HIV

- Risk groups identified
  - MSM
  - Blood recipients
  - IVDU

- ≥ 100 partners/year (implying that 99 are safe...)

- Anal receptive intercourse/fist

- Not using condoms
AIDS Prevention Before HIV

- Exclusion of risk groups from blood donation
- Education/recommendations on the risk factors
AIDS Prevention Before HIV: Effects

- Transfusion associated, transmission dropped
- In certain areas, risk factor transmission dropped, witness the 90% reduction in syphilis in San Francisco
  - Supported by subsequent HIV analysis of banked blood
Bacterial Vaginosis and Prematurity in Indonesia*

- Association between bacterial vaginosis diagnosed at 16 to 20 weeks and preterm delivery (gestational age <37 weeks)
  - OR = 2.0; 95% CI 1.0 - 3.9
  - Above OR adjusted for mother’s age, education, smoking and *Trichomonas*

“Only bacterial vaginosis diagnosed early in the second trimester of pregnancy plays a major role as a risk factor for preterm delivery”

- Clindamycin vaginal cream - an effective treatment

Begin Program in Indonesia?

- PPE
  - Conduct an RCT
    - Corollary to PPE: SE
**Intravaginal Clindamycin for BV: Effects on Preterm Delivery and LBW**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clindamycin</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm (&lt;37)</td>
<td>15.0%</td>
<td>13.5%</td>
<td>1.1 (0.7 - 1.7)</td>
</tr>
<tr>
<td>Preterm (&lt;32)</td>
<td>4.7%</td>
<td>2.6%</td>
<td>1.8 (0.8 - 4.2)</td>
</tr>
<tr>
<td>LBW (&lt;2500gm)</td>
<td>9.0%</td>
<td>6.8%</td>
<td>1.3 (0.8 - 2.4)</td>
</tr>
</tbody>
</table>

Types of Epidemiologic Studies

**Observational:** “natural experience”

- **Descriptive:**
  - like newspaper reporting
  - has no control or comparison group

**Analytic:**

- has a control or comparison group

**Experimental:** investigator controls

- has an exposed or experimental group plus a control or comparison group determined by investigator
During the Emergence of Modern Epidemiology (around 1950)

- Sir Austin Bradford Hill, Sir Richard Doll and colleagues conducted:
  - A case-control study of lung cancer
  - A cohort study of smoking and lung cancer
  - The first RCT in medicine, streptomycin for treatment of TB
Descriptive Studies

- Estimate frequency
- Time trend
- Generate more specific etiologic hypotheses
Observational Analytic Studies

- **Cohort**
  - Exposed Outcome?
  - Not Exposed Outcome?

- **Case-Control**
  - Exposed? Outcome
  - Exposed? Control
Prosp ective Cohort Design

The Present
- Population
- Sample
  - Exposure present
  - Exposure absent

The Future
- Outcome
- No Outcome
Example of a Prospective Cohort Design:
Treatment of Severe Malaria in Children

**The Present**
- Population
- Sample
  - PTX present
  - PTX absent

**The Future**
- Death
- No Death
- Death
- No Death
Case-Control Design

The Past or Present

Exposure present
Exposure absent

The Present

Outcome
Sample of cases
Population with disease (cases)

No Outcome
Sample of controls
Much larger population without disease (controls)
Example of Case-Control Design: Use of Bednets and Severe Malaria in Children

The Past or Present

Bednets present  Bednets absent

The Present

Severe Malaria

Population with disease (cases)

Sample of cases

No Severe Malaria

Sample of controls

Much larger population without disease (controls)
RCT PARADIGM

Population of Interest

Sample (Subset)

Randomize

Unexposed

Exposed

Outcome Assessment

Other Allocation Approach?
RCT PARADIGM

Population of Interest

Child ≤5 year presenting at hospital with severe malaria

Randomize

PTX

Placebo

Outcome Assessment

Death within 7 days
Cohort Studies

Also called:

- Incidence - Incidence can be derived
- Prospective - Study group is followed forward in time
- Longitudinal - Study participants are individually followed
Example of a Prospective Cohort Design: Treatment of Severe Malaria in Children

The Present

Population

Sample

PTX Present

PTX absent

The Future

Death

No Death

Death

No Death
In a cohort study, the outcome has not occurred when the study is started usually...

Retrospective cohort studies are possible
Prospective cohort studies avoid two of the most potent causes of bias in the case-control studies:

- Selection bias in the control group
- Ascertainment bias in measuring exposure

Generally, cohort designs are stronger than case-control
Additional Advantages of Cohort Studies

Because potential causative factors are measured before the outcome occurs, a cohort study can establish that they preceded outcome.
Minimize Losses to Follow-up

- Must minimize losses
- Address procedures for minimizing losses later in the week
Strategies Proffered for Dealing with Lost-to-Follow-Up

- Re-double your efforts to obtain information from a sample of lost-to-follow-up (LFU)
- Compare characteristics at baseline in those LFU with those not LFU
- Best approach: Do not have any LFU
Ascertainment Bias
*(Information Bias)* Potential

Since exposure is likely known by both the participants and study investigators, danger of diagnosis of outcome being influenced by exposure class.
Minimize Ascertainment Bias in Cohort Studies - Determination of Outcomes

- Consistent
- Equal for all exposure groups
- Establish explicit, objective criteria
- Outcomes should be assessed blindly, if possible
CONFOUNDING

<table>
<thead>
<tr>
<th></th>
<th>PTX</th>
<th>PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>No</td>
<td>85</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

RR = \frac{15\%}{45\%} = 0.33
Confounding Bias Occur

- Not hypothetical
- Occurs in both cohort and case-control
- Confounding is confusing and needs convincing
  - Play with numbers
  - See page 37
In this example you suspect:

SES is strongly associated with both PTX and death,

i.e., SES is a Confounder
<table>
<thead>
<tr>
<th></th>
<th>PTX</th>
<th>PTX</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High SES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>No</td>
<td>81</td>
<td>27</td>
<td>10%</td>
</tr>
<tr>
<td>Death</td>
<td>90</td>
<td>30</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Low SES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>42</td>
<td>60%</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>28</td>
<td>60%</td>
</tr>
<tr>
<td>Death</td>
<td>10</td>
<td>70</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Advantages of Cohort Studies

- Efficient with higher incidence (approx. > 20%)
- Excellent for studying rare exposures
- Less opportunity for selection bias and ascertainment bias than case-control studies
- Clear temporal sequence of exposure and outcome
- Obtain incidence rates and relative risk
- Yields more understandable information than c-c
Disadvantages of Cohort Studies

- Contains selection bias and probably more ascertainment bias than an RCT
- With rare outcomes, large sample sizes and relatively expensive to conduct
- Long-term follow-up difficult when the latency period for the outcome is long
- Follow-up may be difficult -- losses affect results
- Exposure status may change during study
At a minimum for a cohort study, address in the protocol:

- Entry criteria
- Definitions of the exposure groups (comparison groups) [and implications for selection bias]
- The planned procedures to achieve retention and follow-up of participants
- Selection and measurement of potential confounding factors
- Endpoint: Next sessions (Methods to ascertain outcomes, including blinding procedures, if any)
Example of a Case-Control Design: Use Bednets and Severe Malaria in Children

**The Past or Present**
- Bednets present
- Bednets absent

**The Present**
- Severe Malaria
- Sample of cases

**Population with disease (cases)**
- Much larger population without disease (controls)

**Sample of controls**
- No Severe Malaria
- Bednets present
- Bednets absent
Case-Control Study

**Strengths:**
- Rare diseases
- Disease with long latency period
- Fewer subjects
- Less Expensive
- Quicker to complete
- Evaluate multiple exposures
### Why Is A Case-Control Study Efficient?

<table>
<thead>
<tr>
<th>Cohort Study</th>
<th>E</th>
<th>E</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>15</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>No Disease</td>
<td>1000</td>
<td>2000</td>
<td>3000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1015</strong></td>
<td><strong>2010</strong></td>
<td><strong>3025</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case-Control Study</th>
<th>E</th>
<th>E</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases Disease</td>
<td>15</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Controls No Disease</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
<td><strong>30</strong></td>
<td><strong>55</strong></td>
</tr>
</tbody>
</table>
Why Is A Case-Control Study Efficient?

**Cohort Study**

- Study Size = 3025
- RR = 3.0 95% CI (1.4 - 6.3) p = .005

**Analogous Case-Control Study**

- Study Size = 55
- OR = 3.0 95% CI (1.0 - 9.0) p = .05
Case-Control Examples

<table>
<thead>
<tr>
<th>Cases</th>
<th>E</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Controls</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># Controls</th>
<th>OR</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>3.0</td>
<td>.87 - 10.6</td>
</tr>
<tr>
<td>60</td>
<td>3.0</td>
<td>1.04 - 8.8</td>
</tr>
<tr>
<td>90</td>
<td>3.0</td>
<td>1.10 - 8.3</td>
</tr>
<tr>
<td>120</td>
<td>3.0</td>
<td>1.14 - 8.0</td>
</tr>
</tbody>
</table>
Greater Chance of Bias in Case-Control Studies

- All of the relevant events, disease and exposure, have already occurred when the study begins

- Two potent sources of bias
  - Bias in ascertaining exposure
  - Selection of a control group
Bias in Case-Control Studies

**Information Bias**
- Information is gathered differently from cases and controls
- Difference related to risk factor
- Recall bias is most common

**Selection Bias**
- Cases and controls are selected differently
- Difference in selection is related to risk factor
Ascertainment Bias in Case-Control Studies

- Data collectors and participants can be prejudiced by knowledge of outcome
  - especially if associations are alleged

- Try to ascertain exposure in an unbiased manner
  - blinding
  - visual aids to stimulate memory
Case-Control Study

Case Definition:

- Define objective criteria for reliable diagnosis of disease
- Know what population you are selecting cases from
  - clinic, hospital, etc.
  - population based
Control Selection:

- Free of disease being studied
- Selection must be independent of exposure being studied
- Controls should represent the population from which cases were selected
- Matching is not what it seems! Generally it is better not to match.
Case-Control Study of Risk Factors for AIDS

Case Selection:
- MSM AIDS cases diagnosed in San Francisco during 1983-1984

2 Control Groups:
- MSM STD clinic patients
- MSM from same neighborhood as cases
STD Clinic Controls (HIV-)
OR = 2.9

Neighborhood Controls (HIV-)
OR = 52.0

### Study Population

<table>
<thead>
<tr>
<th>E</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>0</td>
<td>200</td>
</tr>
<tr>
<td>300</td>
<td>1,100,000</td>
</tr>
</tbody>
</table>

- Is a case-control study always efficient?
- Can a cohort study be more efficient?
Low Incidence of Exposure

Case-Control

<table>
<thead>
<tr>
<th>E</th>
<th>E</th>
<th>10,010</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>10,000</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>100,000</td>
</tr>
</tbody>
</table>
Cohort Study

High Outcome Incidence

<table>
<thead>
<tr>
<th></th>
<th>E</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
<td>110</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Cohort Study
Advantages of Case-Control Studies

- Case-control studies are useful and efficient for studying low frequency outcomes (i.e. approx. <5%)
- Case-control studies are useful for studying health problems with a long latent interval
- With rare outcomes, case-control studies are less time consuming and less expensive than cohort studies
Disadvantages of Case-Control Studies

- Easier to Do  . . . . . . . Wrong

- Prone to more selection bias than cohort studies: control group selection difficult
- Prone to more ascertainment bias than cohort: incomplete records or recall bias
- Cannot determine incidence rates
- By definition, pertinent to one outcome
- Cannot observe temporality of association
At a Minimum, for a Case-Control Study, in the Protocol Include

- Definition of cases
- Selection of the control group(s) [implications for selection bias]
- Selection and measurement of potential confounding factors
- Analogous endpoint: The ascertainment of exposure and the related procedures to minimize ascertainment bias (including whether any blinding would be attempted)
Randomized Controlled Trials

The methodologic standard of excellence for scientific experiments
Epidemiologic Study Designs

- **Cohort**
  
  Exposure $\rightarrow$ Outcome

- **Case-Control**
  
  Outcome $\rightarrow$ Exposure

- **Randomized Controlled (Clinical) Trials (RCT)**
RCT PARADIGM

Population of Interest

Child <5 year presenting at hospital with severe malaria

Randomize

PTX

Placebo

Outcome Assessment

Death within 7 days
COHORT

TROHOC

RANDOMIZED

DEZIMODNAR
Assures Comparability

- In observational studies, statistical methods allow investigators to control for confounding factors
  - Must be measured (ABLE)
Assures Comparability (cont.)

- No statistical method can achieve comparability on unknown or unmeasured factors in analysis phase.
- Random allocation is the only known method to assure comparability.
Comparison of Results from Cohort Study and RCT

Intervention: Exercise in men after M.I.
Outcome: Recurrent M.I.

Cohort: $RR = 0.38 \quad 95\% \ CI \ (0.18 - 0.80) \quad p = 0.006$

RCT: $RR = 1.3 \quad 95\% \ CI \ (0.73 - 2.2) \quad p = 0.20$
## Trials of the Treatment of Acute M.I.

<table>
<thead>
<tr>
<th></th>
<th>RCTs (57)</th>
<th>Non-Random (43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in case-fatality rates at $p &lt; 0.05$</td>
<td>8.8% 58%</td>
<td></td>
</tr>
<tr>
<td>Results favored treatment over controls ($p &lt; 0.05$)</td>
<td>60% 93%</td>
<td></td>
</tr>
<tr>
<td>Mean differences in the case-fatality rates</td>
<td>0.3% $\pm 0.8%$ 10.5% $\pm 1.7%$</td>
<td>($p &gt; 0.05$) ($p &lt; 0.001$)</td>
</tr>
</tbody>
</table>
Hormone Replacement and Therapy
Coronary Heart Disease (CHD)

- Hormones decrease risk of CHD by 35% to 50%, according to 3 different meta-analysis of numerous observational studies
- Especially strong for secondary prevention in women with CHD
RCT of hormone-therapy for secondary presentation of CHD

Relative hazard = 0.99; 95% CI 0.80 - 1.22

No effect of hormone therapy

Recent Women’s Health Initiative RCT in healthy women (JAMA 2002; 288: 321-333)

CHD: HR=1.29; 95% CI 1.02-1.63
Chemotherapy for Carcinoma of the Esophagus*

- A meta-analysis of 8 non-randomized studies found a 68% reduction in death (OR=0.32, 95% CI 0.24 - 0.42)

- A meta-analysis of 12 RCTs found a 4% reduction in death

(OR=0.96, 95% CI 0.75 - 1.22)

On average, non-randomized studies result in overestimates of effect. That bias can, however, go in either direction. That bias can be as large or larger than the effects of worthwhile interventions.

Randomized Trials Require Methodological Rigor

- Improperly conducted RCTs yield biased results
- Researchers must devote assiduous attention to design and conduct of RCTs
- Only properly conducted RCTs will fulfill their promise of minimizing bias
- Separate presentation later in the week
Advantages of Randomized Trials

- First and foremost, the only effective method known to control selection bias
- Controls confounding bias
- Facilitates effective blinding in some trials
- Theoretically attractive - many statistical methods assume random assignment
- Maintains advantages of cohort studies
Disadvantages of Randomized Trials

- May be complex and expensive
- Difficult and expensive with low incidence outcomes.
- May lack representativeness - volunteers may differ from population of interest
- Ethical challenges of experimental research
- Sometimes impossible or impractical
Randomized Controlled Trials

Indeed, the methodological standard of excellence

Thank You