OVERVIEW OF STUDY DESIGN

- Understanding study design is basic to epidemiology
- Certain factors about infectious disease that impact on study design
  - Case can also be an exposure
  - May be multiple means of transmission
  - Studies often take place in a crisis and require rapid assessment

STUDY DESIGN

- Two fundamental tenets
  - Human disease does not occur at random
  - Existence of causal and possibly preventable factors
- Goal of selecting the best study is to identify which will best determine these factors

CHOOSING A STUDY DESIGN

- Consider if disease or exposure is rare
  - Rare exposure – cohort
  - Rare disease – case-control
- Amount of knowledge about a disease
  - Less known, case-control
  - Consider practicality

EPIDEMIOLOGIC TRIANGLE

- Three factors
  - Host
  - Agent
  - Environment
- Biologic variation in either the host or agent can influence the natural history of disease
- Environment can effect transmission
- There may be an alternate host or reservoir of disease (life cycle outside human host)

SAMPLING

- Identify a study sample who are at risk for the disease and are representative of the underlying population
- Sample size needs to be large enough to provide sufficient power
DATA COLLECTION

- Variety of means
  - Interviews, questionnaires, medical record review, medical exams
  - A researcher needs to be able to measure the occurrence of an infection or disease
  - Can be costly and difficult
  - Develop a standardized case definition

DATA COLLECTION (CONT)

- Identify and measure infection or disease
  - Biological marker, such as antibodies
  - Immunity waned vs. never existed
  - Exposed vs. vaccinated
  - Disease vs. infection
  - Case-definition based upon symptoms

DATA SOURCES

- Laboratory testing
- Symptom based case definition
- Personal interview
- Pre-existing data
  - Death certificates
  - ICD 9 Codes
  - Pathology reports

DISEASE IDENTIFICATION AND DATA SOURCE

VARIOUS DESIGNS

- Case reports, case series
- Ecological
- Cross-sectional
- Case-control
- Cohort
- Clinical trial
- Variations: nested studies, serial cross-sectional, etc.

HIERARCHY OF EPI DESIGNS
**DESCRIPTIVE STUDIES**

- Describe the nature of the disease, e.g. the case-fatality.
- Often conducted early in the study of a specific disease.
- Can be hypothesis generating.
- Can provide important information.

**CASE REPORTS**

- Rabies is a zoonotic viral infection spread to humans from an infected animal. Case reports have provided important data about this disease.
- What was the significance of the two case reports presented?
  1) spelunker
  2) child and duck vaccine

**CASE SERIES**

- AIDS cluster
  - Identification of men in NYC with Pneumocystis carinii pneumonia and men with Karpos's sarcoma in San Francisco.
  - Pharmacy aid
  - This case series was central in identifying HIV as a new disease.

**ECOLOGICAL STUDIES**

- Exposure is measured at the population level rather than at the individual level, and correlations are identified.
- Subject to the ecological fallacy.
ANALYTIC STUDIES

- Purpose is to identify associations between risk factors and diseases or treatments and disease outcome.
- Differences in designs are based on:
  - Temporal nature
  - How subjects are selected
  - Measures of association

MEASURES OF ASSOCIATION

- Calculation of association is dependent upon the study design.
- Keep in mind you are calculating both the strength of association and the statistical significance.
- The odds ratio is an estimate of the relative risk when the disease is rare and the controls are representative of the underlying population. This may not be the case if one is studying a more common disease, such as a rhinovirus (common cold).

CROSS SECTIONAL STUDIES

- Identification of disease and exposure at the same time
- HAV and household characteristics on US/Mexico border
- Serial cross-sectional studies to determine trends
  - e.g., Newborn screening for HIV

CASE-CONTROL STUDIES

- Participants identified on the basis of disease status:
  - Outbreak investigations
  - Able to test for multiple associations
  - Can also test a specific hypothesis
  - Good for rare diseases or diseases with a long latency period
  - More subject to biases

CASE-CONTROL EXAMPLE

- Reye’s syndrome and aspirin exposure
  - Found that children treated with aspirin for viral infections, such as influenza and chicken pox, were significantly more likely to develop Reye’s Syndrome.
  - Subsequently, parents were warned not to give children aspirin and Reye’s syndrome has virtually disappeared. See Figure 3-10.

NESTED CASE-CONTROL STUDIES

- Case-control study within an existing cohort study
- May overcome issues in determining exposure as exposure information is collected as part of the original cohort study
- Allows for more targeted analysis of stored specimens
  - Density sampling
  - Case-cohort design
**EXAMPLE OF A NESTED CASE-CONTROL STUDY**

- Epstein-Barr Virus (EBV) Infection and Hodgkin’s Disease
- Washington County, Md.
- Sera repository from individuals who developed EBV for 20 years starting in 1963
- Specimens were collected from cases and matched with controls
- Found a significant association of EBV and HD

**EXAMPLE OF A COHORT STUDY**

- Several HIV cohort studies are presented
- ALIVE study, for example
  - Cohort of 2960 individuals
  - Individuals using injection drugs
  - Free of HIV at baseline
  - HIV was highest among females who continued using drugs and lowest among those who stopped using drugs

**NESTED COHORT STUDY**

- Existing cohort study
- Subgroup of participants are selected based upon a given exposure
- Differs from nested case-control study as the subgroup of participants are selected based on disease

**CLINICAL TRIALS**

- Generally used to evaluate a treatment or preventive measure, e.g. vaccination
- Considered the gold standard because of more investigator control
  - But they may have select population and not reflect real world implementation
- Characteristics include
  - Randomization
  - May have blinding (single, double, triple)
  - Can include placebo control or usual practice

**CLINICAL TRIAL EXAMPLE**

- HIVNET trial
  - Use of zidovudine (AZT) therapy among pregnant women to prevent HIV infection in infants
  - Rates: AZT group: 8.3%
  - Control group 25.5%
  - Study had such dramatic results (67.5% reduction in transmission) that it was stopped early and all participants received the drug.
SPECIAL FACTORS

- Biologic variation in either the agent or host (or both) can influence disease
- Can be difficult to identify exact time of transmission
  - HIV study among blood recipients
    - Had an exact date of exposure
    - Could compare progression rates of donors with recipients
    - Demonstrated that there are viral characteristics impacting HIV transmission
- There are also studies of repeatedly HIV exposed individuals who do not develop AIDS which look at host factors

SPECIAL STUDIES

- Twin studies
- Genetic studies
- Meta-analysis

META-ANALYSIS

- Statistical analysis of a collection of studies
  - Used to synthesize data across sometimes controversial studies or when individual studies are under-powered
  - Issues with publication bias as more positive associations are more likely to be published
  - Difficulty in combining studies with important differences in exposure and/or outcome measures
    - E.g., Diagnostic vs. laboratory identification of disease