DISEASE DETECTIVES – PART TWO
OUTBREAK INVESTIGATION

Steps in Solving Health Problems
- o Step 1-Collect Data ó Surveillance, determine Time/Place/Person triad
- o Step 2- Assessment- Inference
- o Step 3- Hypothesis testing ó Determine how and why
- o Step 4- Action-Intervention

Epidemiology Studies ó Types of Experimental Studies and Observational Studies
- **Experimental**-
  - o *Clinical Trials* for Individuals
  - o *Community Trials* for Communities
- **Observational**
  - o *Cohort Study*- the epidemiologist records whether each study participant is exposed or not, and then tracks the participants to see if they develop the disease of interest
  - o *Case Control Study* - investigators start by enrolling a group of people with disease (case-patients) and a comparison group without the disease (control) to compare previous exposure between the groups
  - o *Cross Sectional Study* - a sample of persons from a population is enrolled and their exposures and health outcomes are measured simultaneously-it tends to assess the presence (prevalence) of the health outcome at that point of time without regard to duration.
  - o *Ecological Study (Div C)* - a study in which at least one variable, either an exposure or the outcome, is measured at the group (not individual) level. Examples of group-level measures include the incidence rate of cancer among a specific population, the mean level of blood pressure of patients seen at a clinic, the average sunlight exposure at specific geographic location on the earth, or even a preventive service included in a health insurance plan. The occurrence of disease is compared between groups that have different levels of an exposure, which affords this study design to have at least one comparison group.

Scientific Method as related to Disease Detectives

Compare Scientific Method to the Steps in Outbreak Investigation
- Obtain Background Information
- Define the Problem
- Formulate Hypothesis
- Develop a Study to Test the Hypothesis
- Collect Data and Observations
- Evaluate Results
- Determine if Hypothesis is true/modify ó Do lab verification to prove hypothesis
- Formulate Conclusions
- Report Results

STEPS OF AN OUTBREAK INVESTIGATION

Note: This handout will use the 13 Steps outlined in
http://www.cdc.gov/ophss/csels/dsepd/ss1978/

This is a conceptual order – steps may be done at the same time
***- Implement control as soon as the source & mode are suspected!!!!**

Step 1: Prepare for Field Work

1. Research, supplies & equipment ó research the disease or situation and gather needed supplies & equipment to conduct the investigation
2. Administrative arrangements ó make official administrative and personal travel arrangements
3. Local contacts - follow protocol and contact all parties to determine roles & local contacts

Step2: Establish the Existence of an Outbreak

Consider severity, potential for spread, public concern, and availability of resources
1. Expected # of cases for area ó use records as health dept., hospital records, death records, physician records, doctor survey to determine expected # for the area in a given time
2. Other factors in play ó numbers may exceed normal due to factors such as better reporting, seasonal fluctuations, population changes

Step 3: Verify the Diagnosis

1. Proper diagnosis- verify the procedures used to diagnose the problem and check methods used for identifying infectious and toxic chemical agents
2. Not lab error ó be sure that the increase number of cases are not due to experimental error
3. Commonality ó interview several persons who became ill to gain insight concerning possible cause, source, and spread of disease or problem
4. Diagnosis may not be known initially. Need to screen ill persons, collect clinical and environmental samples and get them tested in order to determine agent

Step 4: Construct a working case definition

1. Case definition ó establish with the 4 components or standard criteria for determining who has the disease or condition
   a. Clinical information ó about the disease or condition
   b. Characteristics- of the affected people
   c. Location or place- as specific as possible as restaurant, county, or several specific areas
   d. Time sequence- specific time during which the outbreak or condition occurred
2. Identification of specific cases ó kind & number ó count specific cases
   a. Confirmed ó have diagnosis with case definition plus lab verification
   b. Probable ó many factors point to diagnosis but may lack lab verification
   c. Possible ó some factors point to diagnosis
   Note: Initial reports may be only a small sampling of the total problem. Be sure to expand search to determine the true size and extent of the problem.

3. Line Listing ó chart of specific cases including information about each case

    a. Identifying information- ID or case # - left column + name or initials
    b. Clinical information ó diagnosis, symptoms, lab results, hospital ó death?
    c. Descriptive: time ó date & time of onset + date of report
    d. Descriptive: person ó age, sex, occupation, other characteristics
    e. Descriptive: place ó street, city or county + specific site
    f. Risk factors & possible causes ó specific to situation (disease) and outbreak setting

Sample Line Listing from six case report forms on a wedding reception outbreak

ID #	Initial	Date-Onset	Diagnosis	How Confirmed	Age	Sex	County	Physician	Cleveland-M Kay Wedding
1	KR	7/23	probable trichinosis	Not done	29	M	Columbia	Goodman	Yes
2	DM	7/27	trichinosis	Biopsy	33	M	Columbia	Baker	Yes
3	JG	8/14	probable trichinosis	Not done	26	M	Columbia	Gibbs	Yes
4	RD	7/25	trichinosis	Serologia	45	M	King	Webster	Yes
5	NT	8/4	trichinosis	Not done	27	F	Columbia	Stanley	Yes
6	AM	8/11	R/Otrichinosis	Pending	54	F	Clayton	Mason	Yes

Step 5: Find cases systematically and record information

Case finding may be done through passive reporting, screening, records review

The data collection form should include the following types of information about each case.

- **Identifying information**. A name, address, and telephone number is essential if investigators need to contact patients for additional questions and to notify them of laboratory results and the outcome of the investigation. Names also help in checking for duplicate records, while the addresses allow for mapping the geographic extent of the problem.
- **Demographic information**. Age, sex, race, occupation, etc. provide the **person** characteristics of descriptive epidemiology needed to characterize the populations at risk.
- **Clinical information**. Signs and symptoms allow investigators to verify that the case definition has been met. Date of onset is needed to chart the time course of the outbreak. Supplementary clinical information, such as duration of illness and whether hospitalization or death occurred, helps characterize the spectrum of illness.
- **Risk factor information**. This information must be tailored to the specific disease in question. For example, since food and water are common vehicles for hepatitis A but not hepatitis B, exposure to food and water sources must be ascertained in an outbreak of the former but not the latter.
- **Reporter information**. The case report must include the reporter or source of the report, usually a physician, clinic, hospital, or laboratory. Investigators will sometimes need to contact the reporter, either to seek additional clinical information or report back the results of the investigation.

Step 6: Perform Descriptive Epidemiology - Describe and Orient the Data in Terms of Time, Place and Person

Multiple forms may be used in the course of a single outbreak investigation. May start out with broad, open-ended questions designed to generate hypotheses and then become more specific as investigation progresses.
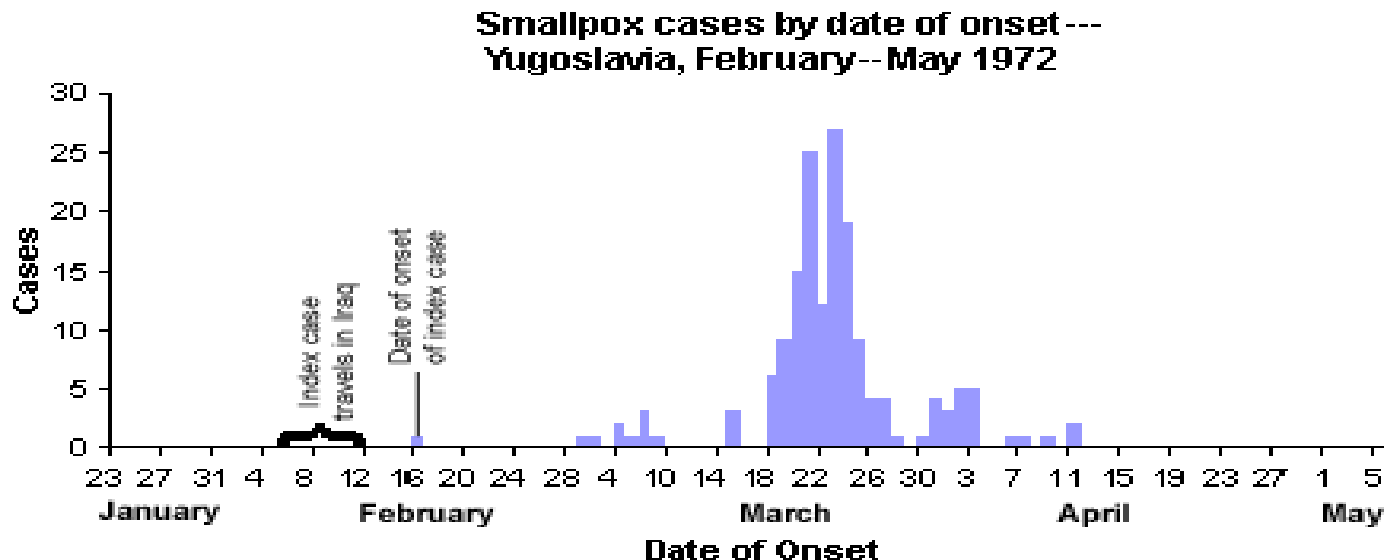
Time, Place and Person ó describes disease or health situation

> **TIME** - <u>Epidemic Curve or Epi curve</u> (Begin early & update often) ó a histogram showing
> the course of the disease or outbreak to identify the source of the exposure
> (x axis=units of time equal to 1/4 to 1/3 incubation time and y axis = # of cases)
> Note: a single point or source will have only one peak, a plateau will show a
> continuous common source, several uniform peaks will indicate a propagated outbreak
> spread from person to person
>
> **PLACE** ó geographic extent plus spot map of cases to identify groups specific to a location
> or environmental factors
>
> **PERSON**óidentify the affected population by type of person or by exposures as age, sex,
> high risk exposure as with AIDS

Sample EPI or Epidemic Curve

Smallpox cases by date of onset --- Yugoslavia, February--May 1972

Step 7: Develop Hypotheses (<u>Agent/host/environment triad</u>) = chain of transmission

1. Agent /host /environment = agent capable of causing disease & its source +
   host or persons susceptible to agent + environment allowing them to get together
   Infectious Groups: viruses, bacteria, protistans (protozoa), fungi, animals **(**worms)
2. Testable ó hypothesis must be in a form that is testable
3. Current knowledge & background ó it should be based upon current knowledge
   and be updated or modified as new information is uncovered!!!

Step 8: Evaluate Hypotheses Epidemiologically – Analytical Epidemiology ** Must have a control group**

1. Compare with established fact ó these are used when evidence is strong and clear cut
2. **Must have lab verification to validate a hypothesis**.
3. Two types of Studies: (Study determinants of health problems ó how & why)
   a. <u>**Cohort**</u> ó Based upon ***exposure status*** whether or not they have outcome (illness);
      used with a small well-defined population and moves forward from exposure.
    Both groups have a known exposure and are checked for future outcomes or illness.
      <u>retrospective</u>:(historic cohort) starts at exposure in past & moves forward to outcome
      <u>prospective</u>: starts a present exposure and moves forward in time to outcome
          (Calculations = attack rate and relative risk or risk ratio)
   <u>Sample using 2 X 2 table</u>: 400 people attended a special awards dinner.
      Some persons became ill. The suspected culprit was the potato salad.
      The population at the dinner was then surveyed to determine who became ill.

	Disease Yes	Disease No
Exposed (Ate salad)	150 **(a)**	30 **(b)**
Unexposed (no salad)	50 **(c)**	170 **(d)**

   <u>Attack rate</u> ó the rate that a group experienced an outcome or illness (a special form of
   incidence-time factor is often overlooked if it is short)
         = number sick ÷ total in that group
      (Look for high attack rate in exposed & low rate in unexposed)
            exposed = a ÷ (a+b) = 150 ÷ 180 = 80%
            unexposed = c ÷ (c + d) = 50 ÷ 220 = 20%
      Relative risk = [a ÷ (a+b)] / [c ÷ (c+d)] = 80% ÷ 20% = 4

1. Relative risk estimates the extent of the association between an exposure and a disease. It estimates the likelihood of developing the disease in the exposed group as compared to the unexposed group.
2. A relative risk = 1.0 indicates that the incidence rates of disease in the exposed group is equal to the incidence rates in unexposed group. Therefore the data does not provide evidence for an association.
3. A relative risk >1.0 indicates a positive association or an increased risk. This risk increases in strength as the magnitude of the relative risk increases.
4. The data indicates a negative association or decreased risk (possible protective effect) if the relative risk is between 0 and 1.0. Relative risk is not expressed in negative numbers.

Note: Relative risks are used only in cohort studies. May see odds ratio used for some cohort studies in the literature. This is because some stratification methods used to control for the effect of other variables result in estimates of the odds ratio.

b. **[Case-Control](#)** - Works ***backward from effect or illness*** to suspected
     cause. Control group is a selected group who has similar characteristics
     to the sick group but is not ill. They are then checked for similar
     exposures. It is often hard to select the control group for this type of study.
     Odds Ratio is calculated to evaluate the possible agents & vehicles of transmission.

$$\textbf{\textit{Odds Ratio}} = \frac{\text{Odds of exposure in cases}}{\text{Odds of exposure in controls}} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

a = # of case patients exposed   **b** = # of control exposed
c = # of case patients unexposed   **d** = # of control unexposed

Sample: Several patients were diagnosed with Hepatitis A. The
local Restaurant A was thought to be the source of the infection.
40 case patients and a similar disease free group or control were
contacted to determine if they **ate** at Restaurant A.

2 X 2 table of data:

	Case patients	Controls	Total
Yes	**a** = 30	**b** = 36	66
No	**c** = 10	**d** = 70	86
Total	40	106	146

The odds ratio for Restaurant A is thus $30 \times 70 / 36 \times 10 = 5.8$. This means that people who ate at Restaurant A   were 5.8 times more likely to develop hepatitis A than were people who did not eat there.

Potential Types of Error in Experimental Design and Data Collection (Div C)

- False Relationships
    - **Random Error** - the divergence due to chance alone, of an observation on sample from the true population value, leading to lack of precision in measurement of association
    - **Bias** or **systematic error** in an epidemiologic study that results in an incorrect estimation of the association between exposure and health-related event

- Non-Causal Relationships ó õguilt by associationö
    - **Confounding** ó occurs when the effects of two risk factors are mixed in the occurrence of the health-related event under study - when an extraneous factor is related to both disease and exposure

Random Error:
- Is the result of fluctuations around a true value due to sampling variability
- It can occur with data collection, coding, transfer, or analysis of data
- Affects measurement in a inconsistent manner
- Ways to reduce random error may include ó increasing the sample size and reduce the variability in measurements

Systematic Error:
- Occurs when there is a difference between the true value (the population) and the observed value (the sample)
- The error is in the system used for measurement so it occurs in each occasion hence systematic error
- Conclusions drawn on this data will be inaccurate ó too great or too little
- Validity of a study depends upon the degree of systematic error ó less error equals more validity
  - <u>Internal validity</u> ó the amount of error in measurements including those for exposure, disease, and the association between these variables.
  - <u>External validity</u> órelates to the process of generalizing the finding of a study to the population from which the study is taken

Types of Bias: Describe problems in how the study is organized
- **Selection bias –** occurs when study subjects are selected for the study as a result of a third unmeasured variable which is association with both the exposure and the outcome. There may be association between diseases or between characteristics and a disease related to the admission to a hospital for those with a disease, without the disease but with symptoms, and those with only the characteristics of the disease.
- **Information bias –** occurs from systematic error in the assessment of a variable. Examples **are information bias, response bias, interviewer bias, recall bias**

Confounding: the co-occurrence or mixing of effects of extraneous factors
- May lead to overestimating or underestimating the true association between exposure and outcome.
- A **confounding variable** would be a variable (pollution) that can cause the disease under study (cancer) and is also associated with the exposure (smoking).

Step 9: As necessary, Reconsider, Refine, and Re-evaluate Hypotheses
1. No confirmation of hypothesis - where analytical studies do not confirm hypothesis May need to look for a new vehicle or mode of transmission
2. More specific ó May need to be more specific in makeup of case patients & controls
3. May find illness associated with one source (i.e. restaurant A). Develop and test a refined hypothesis about how contaminated food got into restaurant A. Screening staff may or may not answer the question as infected staff may represent additional cases.

Step 10: Compare and Reconcile with laboratory and/or environmental studies
Verify with environmental/laboratory studies - verification with controlled conditions is very important.
1. Epidemiology can implicate vehicles and guide appropriate health care action
2. Laboratory evidence can confirm the findings *LAB VERIFICATION NEEDED TO VALIDATE HYPOTHESIS.*
3, Environmental studies are equally important in some settings and can be helpful in explaining why an outbreak occurred. Examination of the area of an outbreak can provide evidence and clues used in laboratory analysis.
4. Isolating the same pathogen from a case patient and epi-linked source is supportive. Failure to do so may mean you have the wrong bug, the wrong association or lab problem.

Bradford Hill criteria for Verifying the Cause of the Health Problem

1. Strength of the association.

According to Hill, the stronger the association between a risk factor and outcome, the more likely the relationship is to be causal. (Use and interpretation of analytic statistics ó Div C)

2. Consistency of findings.

Have the same findings must be observed among different populations, in different study designs and different times?

3. Specificity of the association.

There must be a one to one relationship between cause and outcome.

4. Temporal sequence of association.

Exposure must precede outcome.

5. Biological gradient.

Change in disease rates should follow from corresponding changes in exposure (dose-response).

6. Biological plausibility.

Presence of a potential biological mechanism.

7. Coherence.

Does the relationship agree with the current knowledge of the natural history/biology of the disease?

8. Experiment.

Does the removal of the exposure alter the frequency of the outcome?

Step11: Implement Control and Prevention Measures – as soon as possible!!

1. As soon as source is known ó people are sick or hurting and need help; must know agent & source of agent + susceptibility of host+ chain of transmission; can find standard prevention and control measures for many infectious diseases; impact of measures should reflect seriousness of the condition and strength of evidence

2. Aim at chain of agent-source-host ó break the chain of transmission at any of its 3 points

3. May interrupt transmission or exposure ó with vehicles as isolation

4. May reduce susceptibility ó with immunization, legal issues and/or education

Step 12: Initiate or maintain surveillance

1. Once control and prevention measures have been implemented, they must continue to be monitored

2. If active surveillance was initiated as part of case finding efforts, it should be continued to determine whether the prevention and control measures are working

   o What is happening to the number of new cases?

   o Has the outbreak spread outside its original area or the area where the interventions were targeted?

   o If so, effective disease control and prevention measures need to be implemented in the areas.

Step 13: Communicate Findings

1. Oral briefing ó inform local health officials or other need-to-know groups as soon as information is available

2. Written report ó usually done in scientific format for future reference, legal

3. Can be an important part of control measures. õDo not eat watermelon from Store A as we have found it may contain Salmonella issues, and education *Many health departments strive to communicate directly with the public, usually through the media, both during an investigation and when the investigation is concluded*