### 2017 DISEASE DETECTIVES (B&C) TRAINING HANDOUT

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**DISCLAIMER** - This presentation was prepared using draft rules. There may be some changes in the final copy of the rules. The rules which will be in your Coaches Manual and Student Manuals will be the official rules. **BE SURE TO CHECK THE 2017 EVENT RULES** for EVENT PARAMETERS and TOPICS FOR EACH COMPETITION LEVEL

### **TRAINING MATERIALS:**

- Training Power Point presents an overview of material in the training handout
- Training Handout presents introductory topic content information for the event
- 3 Sample Tournaments with sample problems with key
- Event Supervisor Guide has event preparation tips, setup needs and scoring tips
- Internet Resource & Training Materials are available on the Science Olympiad website at www.soinc.org under Event Information.
- A Biology-Earth Science CD, a Disease Detectives CD as well as the Division B and Division C Test Packets are available from SO store at www.soinc.org

#### **Event Format:**

- Format and material of the Division B and C event is similar except that the level of reasoning and math skills should be consistent with the grade level.
- Differences between the two levels should be reflected in both the type of questions asked and the scoring rubrics. 2017 emphasis will be foodborne causes of public health problems
- Be sure to check the event parameters in the rules for the resources allowed.
- Format and material of the Division B and C event is similar except that the level of reasoning and math skills should be consistent with the grade level. **Division C may do some statistical analysis not more than 10% of the competition.**
- Differences between the two levels should be reflected in both the type of questions asked and the scoring rubrics.

### **Types of Knowledge**

- Definitions of basic epidemiologic terms
- Categories of disease causing agents
- Modes of disease spread
- Triads of analysis (e.g., person/place/time & agent/host/environment)
- The basis for taking action to control and prevent the spread of disease

### **Epidemiology**

- Studies health of populations instead of individuals
- Uses the scientific method 10 step method of investigating outbreaks
- Studies the distribution and determinants of disease in human populations
- Attempts to prevent and control those diseases
- Health-related events:
  - o chronic diseases
  - o environmental problems
  - o behavioral problems
  - o injuries
  - infectious diseases

# There is a three topic rotation for Disease Detectives: Environmental Quality, Population Growth, and Food Borne Illness – each on a two year rotation

### 2017 Emphasis – Some Causes of Foodborne Causes of Public Health Problems

See the FDA chart and Bad Bug Book v.2 links below.

- Bacteria
- Viruses
- Parasites
- Protozoa
- Natural toxins
- Other pathogenic agents (as Prions)

### Some Population Growth Causes of Public Health Problems

- Water Quality, Water Pollution, Water Demands
- Sanitation Needs
- Growth of Slums and Household Environment
- Environmental Degradation
- Air Pollution
- Infectious Disease Outbreaks
- Rapid Spread of Disease via Public Transportation and Air Travel
- Food Quality and Food Contamination
- Lack of food in poor nations vs. unhealthy fast food and drinks in technological societies
- Availability of health care for the poor and the aged
- People moving into uninhabited areas = new pathogensas Lyme Disease and Ebola

### **Some Environmental Causes of Public Health Problems:**

- Air pollution, Smoking, Inducers of Asthma
- Flooding health problems, Drought problems
- Extreme heat, UV exposure
- Lead contamination, Pesticides, Chemical Spills
- Water pollutants, Heavy metals
- Ventilation pollutants
- Noise induced hearing loss
- Waste and toxic substance
- Food contamination

# Principles of Epidemiology 3<sup>rd</sup> edition from CDC

Http://www.cdc.gov/osels/scientific edu/SS1978/SS1978.pdf

### **Epidemiology Basics published by the World Health Organization**

http://whqlibdoc.who.int/publications/2006/9241547073 eng.pdf

### Causes of Foodborne Illness - Bad Bug Book 2

 $\underline{http://www.fda.gov/Food/FoodborneIllnessContaminants/CausesOfIllnessBadBugBook/default.htm}$ 

The chart below includes foodborne disease-causing organisms that frequently cause illness in the United States. As the chart shows, the threats are numerous and varied, with symptoms ranging from relatively mild discomfort to very serious,life-threatening illness. While the very young, the elderly, and persons with weakened immune systems are at greatest risk of serious consequences from most foodborne illnesses, some of the organisms shown below pose grave threats to *all* persons. <a href="http://www.fda.gov/Food/ResourcesForYou/Consumers/ucm103263.htm">http://www.fda.gov/Food/ResourcesForYou/Consumers/ucm103263.htm</a>

Organism	Common Name of Illness	Onset Time After Ingesting	Signs & Symptoms	Duration	Food Sources
Bacillus cereus	B. cereus food poisoning	10-16 hrs	Abdominal cramps, watery diarrhea, nausea	24-48 hours	Meats, stews, gravies, vanilla sauce
Campylobacter jejuni	Campylobacteriosis	2-5 days	Diarrhea, cramps, fever, and vomiting; diarrhea may be bloody	2-10 days	Raw and undercooked poultry, unpasteurized milk,contaminated water
Clostridium botulinum	Botulism	12-72 hours	Vomiting, diarrhea, blurred vision, double vision, difficulty in swallowing, muscle weakness. Can result in respiratory failure and death	Variable	Improperly canned foods, especially home- canned vegetables, fermented fish, baked potatoes in aluminum foil
Clostridium perfringens	Perfringens food poisoning	8–16 hours	Intense abdominal cramps, watery diarrhea	Usually 24 hours	Meats, poultry, gravy, dried or precooked foods, time and/or temperature-abused foods
Cryptosporidium	Intestinal cryptosporidiosis	2-10 days	Diarrhea (usually watery), stomach cramps, upset stomach, slight fever	May be remitting and relapsing over weeks to months	Uncooked food or food contaminated by an ill food handler after cooking, contaminated drinking water
Cyclospora cayetanensis	Cyclosporiasis	1-14 days, usually at least 1 week	Diarrhea (usually watery), loss of appetite, substantial loss of weight, stomach cramps, nausea, vomiting, fatigue	May be remitting and relapsing over weeks to months	Various types of fresh produce (imported berries, lettuce, basil)
'	E. coli infection ) (common cause of "travelers' diarrhea")	1-3 days	Watery diarrhea, abdominal cramps, some vomiting	3-7 or more days	Water or food contaminated with human feces
E. coli O157:H7	Hemorrhagic colitis or <i>E. coli</i> O157:H7 infection	1-8 days	Severe (often bloody) diarrhea, abdominal pain and vomiting. Usually, little or no fever is present. More common in children 4 years or younger. Can lead to kidney failure.	5-10 days	Undercooked beef (especially hamburger), unpasteurized milk and juice, raw fruits and vegetables (e.g. sprouts), and contaminated water
Hepatitis A	Hepatitis	28 days average (15- 50 days)	Diarrhea, dark urine, jaundice, and flu-like	Variable, 2 weeks-3 months	Raw produce, contaminated drinking water, uncooked foods and cooked foods that are not reheated after

Organism	Common Name of Illness	Onset Time After Ingesting	Signs & Symptoms	Duration	Food Sources
					contact with an infected food handler; shellfish from contaminated waters
Listeria monocytogenes	Listeriosis	gastro- intestinal symptoms, 2-6 weeks	Fever, muscle aches, and nausea or diarrhea. Pregnant women may have mild flulike illness, and infection can lead to premature delivery or stillbirth. The elderly or immunocompromised patients may develop bacteremia or meningitis.	Variable	Unpasteurized milk, soft cheeses made with unpasteurized milk, ready-to-eat deli meats
Noroviruses	Variously called viral gastroenteritis, winter diarrhea, acute non- bacterial gastroenteritis, food poisoning, and food infection	12-48 hrs	Nausea, vomiting, abdominal cramping, diarrhea, fever, headache. Diarrhea is more prevalent in adults, vomiting more common in children.	12-60 hrs	Raw produce, contaminated drinking water, uncooked foods and cooked foods that are not reheated after contact with an infected food handler; shellfish from contaminated waters
Salmonella	Salmonellosis	6-48 hours	Diarrhea, fever, abdominal cramps, vomiting	4-7 days	Eggs, poultry, meat, unpateurized milk or juice, cheese, contaminated raw fruits and vegetables
Shigella	Shigellosis or Bacillary dysentery	4-7 days	Abdominal cramps, fever, and diarrhea. Stools may contain blood and mucus.	24-48 hrs	Raw produce, contaminated drinking water, uncooked foods and cooked foods that are not reheated after contact with an infected food handler
Staphylococcus aureus	Staphylococcal food poisoning	1-6 hours	Sudden onset of severe nausea and vomiting. Abdominal cramps. Diarrhea and fever may be present.	24-48 hours	Unrefrigerated or improperly refrigerated meats, potato and egg salads, cream pastries
Vibrio parahaemolyticu	V. parahaemolyticus s infection	4-96 hours	Watery (occasionally bloody) diarrhea, abdominal cramps, nausea, vomiting, fever		Undercooked or raw seafood, such as shellfish
Vibrio vulnificus	V. vulnificus infection	1-7 days	Vomiting, diarrhea, abdominal pain, bloodborne infection. Fever, bleeding within the skin, ulcers requiring surgical removal. Can be fatal to persons with liver disease or weakened immune systems.	2-8 days	Undercooked or raw seafood, such as shellfish (especially oysters)

### **Basic Epidemiology Terms**

<u>Outbreak</u> – (localized epidemic) – more cases of a particular disease than expected in a given area or among a specialized group of people over a particular period of time.

**Epidemic** – large numbers of people over a wide geographic area affected.

<u>Cluster</u> –an aggregation of cases over a particular period esp. cancer & birth defects closely grouped in time and space regardless of whether the number is more than the expected number. (often the expected number of cases is not known.)

<u>pandemic</u> -An <u>epidemic</u> occurring over a very wide area (several countries or continents) and usually affecting a large proportion of the population.

<u>risk</u> - The probability that an individual will be affected by, or die from, an illness or injury within a stated time or age span.

<u>vector</u> - an animate intermediary in the <u>indirect transmission</u> of an <u>agent</u> that carries the agent from a <u>reservoir</u> to a susceptible <u>host</u>. An organism that transmits the infection as a mosquito transmits the malaria protozoans.

**fomite** - a physical object that serves to transmit an infectious agent from person to person.

A comb infested with one or more head lice would be a fomite or the dust particles containing infectious cold virus that remain after droplets of infected saliva are coughed into the air.

**zoonosis** - An infectious disease that is transmissible from animals to humans.

**surveillance** - The systematic, ongoing collection, analysis, interpretation, and dissemination of health data. The purpose of public health surveillance is to gain knowledge of the patterns of disease, injury, and other health problems in a community so that we can work toward controlling and preventing them.

#### Scientific Method as related to Disease Detectives

### Compare Scientific Method to 10 Steps in Outbreak Investigation

- Obtain Background Information (Steps 1-3)
- Define the Problem (Step 4-5)
- Formulate Hypothesis (Step 6)
- Develop a Study to Test the Hypothesis (Step 7)
- Collect Data and Observations (Step 7)
- Evaluate Results (Step 7)
- Determine if Hypothesis is true/modify (Step 8)
- Formulate Conclusions (Step 9)
- Report Results (Step 10)

### 10 STEPS OF AN OUTBREAK INVESTIGATION

Field investigation of disease or health condition

\*\*- Implement control as soon as the source & mode are known!!!!

This is a conceptual order – steps may be done at the same time

### **Step 1: Prepare for Field Work**

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

# Step 2: Establish the Existence of an Outbreak – consider severity, potential for spread, public concern, and availability of resources

- 1. Expected # of cases for area 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 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 be sure that the increase number of cases are not due to experimental error
- 3. Commonality interview several persons who became ill to gain insight concerning possible cause, source, and spread of disease or problem

### Step 4: Define and Identify Cases – case definition and line listing

- 1. <u>Case definition</u> establish with the 4 components or standard criteria for determining who has the disease or condition
  - a. Clinical information 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 kind & number count specific cases
  - a. Confirmed have diagnosis with case definition plus lab verification
  - b. Probable many factors point to diagnosis but may lack lab verification
  - c. <u>Possible</u> 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 chart of specific cases including information about each case
  - a. Identifying information- ID or case # left column + name or initials
  - b. Clinical information diagnosis, symptoms, lab results, hospital death?
  - c. Descriptive: time date & time of onset + date of report
  - d. Descriptive: person age, sex, occupation, other characteristics
  - e. Descriptive: place street, city or county + specific site
  - f. Risk factors & possible causes specific to situation (disease) and outbreak setting

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

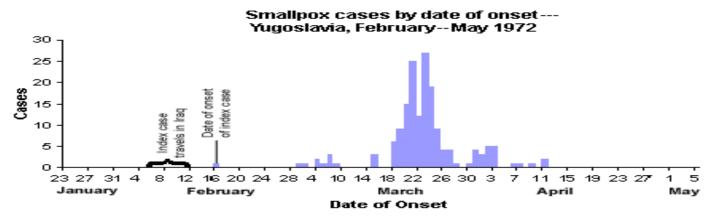
ID#	Initials	Date	Diagnosis	How	Age	Sex	County	Physician	Cleveland-
		Onset		nfirmed					cKay
									edding
1	KR	7/23	probable trichinosis	Not done	29	M	Columbia	Goodman	Yes
2	DM	7/27	trichinosis	Biopsy	33	M	Columbia	Baker	Yes
3	JG	8/14	probable trichinosis	Not done	26	M	Columbia	Gibbs	Yes
4	RD	7/25	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: Describe and Orient the Data in Terms of <u>Time, Place and Person</u> – Descriptive Epidemiology

- 1. Time, Place and Person describes disease or health situation
  - TIME Epidemic Curve or Epi curve (Begin early & update often) 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** geographic extent plus spot map of cases to identify groups specific to a location or environmental factors
  - **PERSON**—identify the affected population by type of person or by exposures as age, sex, high risk exposure as with AIDS

### Sample EPI or Epidemic Curve



- 2. <u>Types of Descriptive Studies</u> Study the distribution of a problem by cases or outcome, frequency in population, exposure, time pattern or environmental factor (Studies without a control group can be used for descriptive purposes!)
  - a. <u>Case report/case series</u> case report = detail report of a single patient from one or more doctors while case series = characteristics of several patients
  - b. <u>Correlative studies</u> correlates general characteristics of the population with health problem frequency with several groups during the same period of time <u>Time series analysis</u> correlate within the same population at different point in time

Ecologic relations – correlate relative to specific ecologic factors as diet

c. <u>Cross sectional</u> - a survey of a population where participants are selected irrespective of exposure or disease status

## Step 6: Develop Hypotheses (Agent/host/environment triad) = 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 hypothesis must be in a form that is testable
- 3. Current knowledge & background it should be based upon current knowledge and be updated or modified as new information is uncovered!!!

### Step 7: Evaluate Hypotheses – Analytical studies \*\* Must have a control group\*\*

- 1. Compare with established fact these are used when evidence is strong and clear cut
- 2. Must have lab verification to validate a hypothesis.
- 3. Two types of <u>Studies</u>: (Study determinants of health problems how & why)
  - a. <u>Cohort</u> 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. <a href="retrospective">retrospective</a>:(historic cohort) starts at exposure in past & moves forward to outcome <a href="prospective">prospective</a>: starts a present exposure and moves forward in time to outcome

(Calculations = attack rate and relative risk)

Sample using 2 X 2 table: 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 <b>(a)</b>	30 <b>(b)</b>
<b>Unexposed</b> (no salad)	50 <b>(c)</b>	170 <b>(d)</b>

<u>Attack rate</u> – the rate that a group experienced an outcome or illness

= number sick ÷ total in that group

(Look for high attack rate in exposed & low rate in unexposed)

exposed = 
$$a \div (a+b) = 150 \div 180 = 80\%$$
  
unexposed =  $c \div (c+d) = 50 \div 220 = 20\%$   
**Relative risk** =  $[a \div (a+b)] / [c \div (c+d)] = 80\% \div 20\% = 4$ 

- 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.
- 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.

# Odds Ratio = Odds of exposure in cases = a/c = ad Odds of exposure in controls b/d bc

 $\mathbf{a} = \#$  of case patients exposed  $\mathbf{c} = \#$  of case patients unexposed  $\mathbf{d} = \#$  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.

### **Step 8: Refine Hypotheses and Carry Out Additional Studies**

- 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 May need to be more specific in make up of case patients & controls
- 3. Verify with environmental/laboratory studies verification with controlled conditions is very important. LAB VERIFICATION NEEDED TO VALIDATE HYPOTHESIS.

### Step 9: Implement Control and Prevention Measures – as soon as possible!!

- 1. As soon as source is known people are sick or hurting and need help; must know agent & source of agent + susceptibility of host+ chain of transmission
- 2. Aim at chain of agent-source-host break the chain of transmission at any of its 3 points
- 3. May interrupt transmission or exposure with vehicles as isolation
- 4. May reduce susceptibility with immunization, legal issues and/or education

## **Step 10: Communicate Findings (see \*\*\* on page 6 for conclusion criteria)**

- 1. Oral briefing inform local health officials or other need-to-know groups as soon as information is available
- 2. Written report usually done in scientific format for future reference, legal issues, and education

### \*\*\*Criteria to Draw Conclusions about Cause and Effect Relations:

- 1. Temporality cause/exposure must precede effect/outcome
- 2. <u>Consistency</u> observation of association must be repeatable in different populations at different times
- 3. <u>Coherence</u>, 1-1 relationship exposure is always associated with outcome/ outcome is always caused by the specific exposure
- 4. Strength of association relationship is clear and risk estimate is high
- 5. Biological plausibility biological explanation makes sense
- 6. <u>Dose/response</u> (biologic gradient) increasing risk is associated with increasing exposure

Examples of types of performance indicators that could be used in Division B and C events at various levels of competition.

Competition	Division			
Level	Division B (Middle School)	Division C (High School)		
Regional/State	List and recognize examples of different modes of transmission  Calculate health-related rates (attack,	Recognize differences between study designs and types of error.  Calculate measures of risk (e.g. relative risk or odds ratio) when given a description of the study		
	incidence, prevalence, case fatality)  Calculate a simple relative risk and describe what it means	design  Calculate measures based on data that is not given but that can be readily extracted.		
	Interpret epi curves, temporal patterns and other simple graphic presentations of health data	Recognize how gaps in information influence the ability to extend conclusions to the general population.		
	List, discuss and recognize examples of disease causing agents (physical and biological)	Do Statistical Analysis on Data for both Descriptive and Analytical Epidemiology		
	Demonstrate an understanding and ability to use terms such as endemic, epidemic and pandemic; population versus sample, association versus cause.			
	Describe various types of prevention and control strategies (e.g. immunization, behavior change, etc) and situations where they might be used			
National	Understand how units affect the relative magnitude of a set of rates with different units.	Recognize unmentioned factors that may influence results and <b>types of error</b> .  Convert between rates with different basic units		
	Calculate appropriate measures of risk when given the study design	(e.g. incidence per 10000 persons/year to incidence per 100 persons/week).		
	Complete tables when given all data needed to complete calculations.	Propose a means to evaluate the effectiveness of an intervention or control program.		
	Propose a reasonable intervention to a public health problem.	Do Statistical Analysis on Data for both Descriptive and Analytical Epidemiology		
	Recognize gaps in information			

**Sample Tasks:** Develop sample problems for Outbreak Investigation relating to the current year topics and then follow the 10 steps for Investigation the Outbreak to solve the problem. Use the Sample Problem provided to help you get started.

### Potential Types of Error in Data Collection (Div C)

- False Relationships
  - o **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
  - o **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 "guilt by association"
  - Confounding 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 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 too great or too little
- Validity of a study depends upon the degree of systematic error less error equals more validity
  - o <u>Internal validity</u> the amount of error in measurements including those for exposure, disease, and
    - the association between these variables.
  - External validity —relates 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).

# Statistical Concepts for Disease Detectives Division C

## **Descriptive Epidemiology**

- Mean
- Median
- Mode
- Variance
- Standard deviation
- Standard error
- Confidence intervals of means

# **Analytic Epidemiology**

- Z-test
- T-test
- Paired T-test
- Chi-square
- McNemar test for paired data
- Fischers exact test
- Cochran Mantel-Haenszel summary odds ratio