LECTURES IN EPIDEMIOLOGY

FOR MEDICAL STUDENTS

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I. INTRODUCTION

1. Definitions and Basic Concepts:

- Definition of Health; WHO Constitution, 1948: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"
- Community health is the collective health status of the community members, and its determinants.
- Personal versus community health:

	Personal H.	Community H.
Focus	Individual person, male OR female; child OR adult	ALL community members, males AND females, children AND adults ...
Status	Individual is sick or not, woman is pregnant or not, person is alive or not ...	ALWAYS there are sick persons, pregnant women, births & deaths...
Interest	Disease prognosis (cure, improvement ...)	Disease distribution, determinants & outcome.
Objective	Reduce individual sufferings.	Improve community welfare
Provider	Medical specialist	P H team.

- Health is measured and quantified through its converse: disease and death.
- **Epidemiology:**
  - Etymological derivation: Epi = upon, demos = people, ology – science.
  - Definitions The study of factors influencing the occurrence, distribution and maintenance of health i.e. the study of the distribution or extent and type of diseases, injuries, and deaths in human population, and the factors influencing their distribution.
- Quantitative measurement of the extent of disease in a community requires relating:
  - Cases (in well defined terms).
  - Defined population base.

Stated in a fraction or rate:

$$\text{Rate} = \frac{\text{Number of events in an area in a time period}}{\text{Population at risk in the same area \& } period} \times \text{factor}$$

2. Natural History of Disease:

The disease process is a result of the interaction of the agent, environment and host factors. Like a plant for example, the disease has an evolution process, passing through the following stages:

a) Stage of prepathogenesis (Susceptibility)

The disease has not developed but the groundwork is laid by the presence of factors which favour its occurrence. Factors whose presence is associated with an increased likelihood that a disease will develop at a later time are called "risk factors" (predisposing factors in clinical terms).

b) Stages of pathogenesis

i. Stage of presymptomatic diseases There is no manifest disease. but usually pathogenic changes (below the level of clinical horizon) have started to occur, e.g. atheroschlerotic changes in coronary arteries. (Equivalent to incubation period of infectious diseases) .

ii. Stage of clinical diseases Sufficient anatomic or functional changes have occured resulting in recognizable signs or symptoms.

iii. Stage of impairment or disability: Conditions with a residual defect (of short or long duration) which leaves the person disabled.

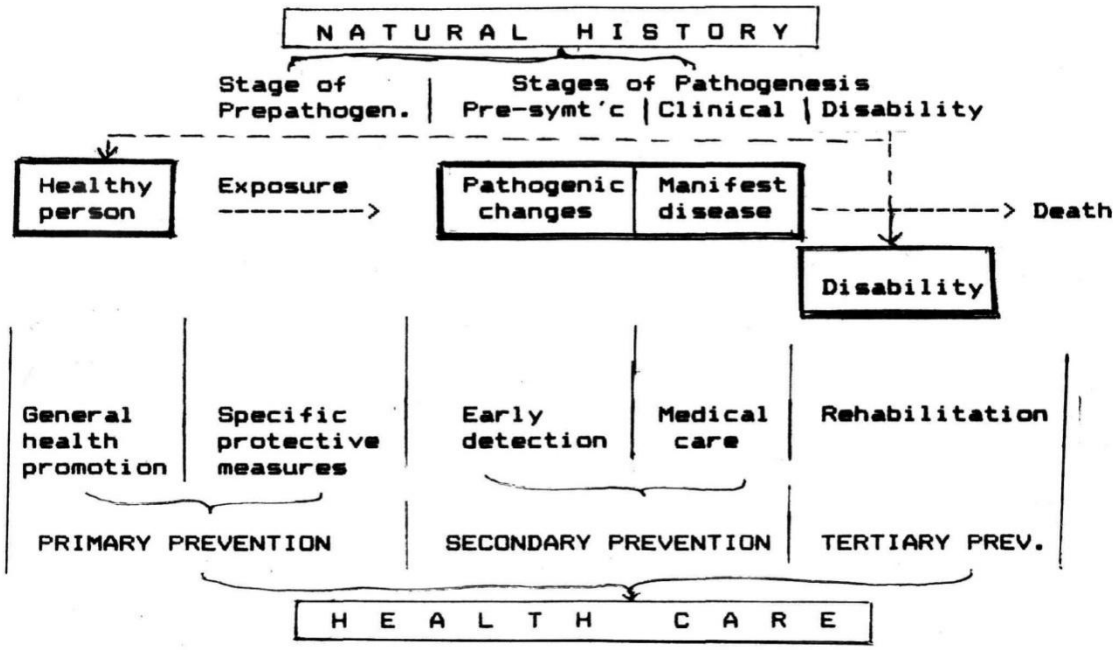
3. Objectives of Epidemiology:

The purpose of epidemiologic study of the risk factors and their distribution is to direct preventive efforts and screening programs to population groups at-risk. The special objectives of epidemiologic investigation are:

a) To determine extent of disease problems in the community.
b) To investigate the etiology of diseases and mode of transmission.
c) To study the natural history of diseases.
d) To develop basis for prevention programs.
e) To evaluate effectiveness of preventive and therapeutic programs.

4. Levels o-f Disease Prevention:

The level of disease prevention, congruent with the stages of the natural history of the disease, are shown in the diagram.



a) Primary prevention: general and specific measures which address:

i. Endogenous (host) factors: genetic, endocrine and immune status

ii. Exogenous (environmental) factors; at:

- Micro-environment: immediate living characteristics e.g. habits (feeding, smoking, exercise ...), shelter, rest, education . . etc .
- Macro-environment: air, water, radiation, roads ... etc.

iii. Specific prevention (include vaccination and chemoprophylaxis).

On conclusion: 1ry prevention include a triad of good nutrition, environmental sanitation and health education.

b) Secondary prevention:

i. Detection of early disease through:

- Screening programs (periodic examination).
- Knowledge of natural history of disease.
- Identification of high-risk groups.

ii. Provision of early medical care to:

- Cure the disease or stop its progression to prevent complications and disability.
- Reverse communicability of infectious diseases (primary prevention for contacts).

c) Teriary prevention: medical, psychosocial and/or vocational rehabilitation, i.e. attempts to restore an affected individual to a usual, satisfying and where possible, self-sufficient role in this community, through:

i. limitation of disability
ii. Maximal utilization of remaining and/or substituted abilities.

To summarize: make best use of what is left.

II. CDMMINCABLE DISEAES

1. The Agent, Environment & Host triad:

a) The agent: is the factor which MUST be present for the disease to occur.

- The disease agent may be present in the:
  (i) Biological environment e.g. microbes and parasites
  (ii) Physical environment e.g. radiation.
  (iii) Chemical environment e.g. lead, asbestos & CO.
  (iv) Social environment e.g. maternal deprivation.
- Infectious agents are biological and range from the simplest viral particles to complex multicellular organisms. The severity of the disease is determined by both agent and host characteristics. Agent characteristics are:

(i) Infectivity = the ability of the agent to get access and lodgement in the host. Measles virus has high infectivity, Leprosis organism has low infectivity.

(ii) Pathogenicity = the ability of the agent to produce tissue damage. Pathogenic!ty is determined by:

- The mechanism of producing tissue reaction, i.e. its ability to:
- Invade tissues e.g. Streptococcosis and Pnemnococcosis.
- Produce toxins e.g. Diphtheria and Tetanus.
- Cause damaging hypersensitive (allergic) reactions e.g. tuberculosis and Streptococcosis.
  - Ability to withstand phagocytosis, to live intracellularly and to produce endotoxin.
  - Immunogenicity (antigenicity) = the ability to induce immunity.

(iii) Virulence = the ability to produce serious illness,which is a measure of the reaction produced. Tb is of low virulence, while Rabies virus is of high virulence.

(iv) Dose: the larger the dose, the higher the chance for the agent to overcome host resistance.

b) <u>The Environment:</u> Environmental factors either:

- Facilitate exposure to the agent; or.
- Enhance susceptibility (= extrinsic factors).

Environmental factors are classified into:

(i) Biological factors: man, animal and plant (animate reservoirs of infection)

(ii) Physical -factors: include:

- Geography: some CD's have de-finite geographic distribution.
- Urban/rural residence.
- Climates: heat, moisture, rain-Fall .... (seasonality).
- Air, atmospheric pressure, radiation
- Water.
- Soil (= inanimate reservoir).

(iii) Chemical factors: include:

- Poisonous materials.
- Nutrients.

(iv) Social environmental -factors: e.g.

- Socio-economic level: income, occupation, education, housing, crowding ... etc.
- Political system.
- Health system.
- Level of technology.
- Social customs and -food habits.
- Receptivity to new ideas.

The ecological interactions are complex, hence measures -for control of disease should be evaluated in terms of the totality of effects they are likely to have on the ecosystem.

(Ecology = the study of the relationship of organisms to each other, as wel1 as to all other aspects of the environment).

c) <u>The Host:</u> The host factors are detrimental to susceptibility to, and severity of disease. Host factors (= intrinsic factors) include:

- Genetic, racial and constitutional factors.
- Age and sex.
- Physiological factors e.g. fatigue, stress, pregnancy.
- Defence mechanism: general (resistance), specific (immunity).
- Habits and personality development (influenced by social and cultural factors).
- Prior medical experience (diseases, injiuries, medical or surgical procedures).

2. Mode of Spread of CD's:

- Transmission of infection involves escape of the infectious agent from a source or reservoir, conveyence to a susceptible host, and entry into that host. Transmission is either:

a) <u>Horizontal transmission:</u>

(i) Common vehicles: food, water and air. An epidemic may result from:

- Single exposure (common vehicle transmission)
- Multiple exposure
- Continuous exposure
- Single exposure common vehicle transmission is characterized by:
    - ✓ Epidemic shows a rapid rise and -fall, within the range of one incubation period i.e. explosive.
    - ✓ Restricted to groups with common exposure.
    - ✓ Infrequent secondary cases.
    - ✓ May be geographic clustering of cases

(ii) Propagated (= progressive): from person to persons transmission is either:

- Direct: Contact Droplet
- Indirect: Animate = vector Inanimate = fomites

b) <u>Vertical transmission:</u> to subsequent generation e.g. congenital Rubella and Syphilis, Leukemia virsuses, AIDS virus and hepatitis B virus.

3. Epidemiologic patterns of CD's:

a) With regard to extent of spread: The disease may be:

(i) Endemic = the constant presence of a disease or infectious agent within a given geographic area, or the usual presence of the disease in such area.

(ii) Hyperendemic = a persistent intense transmission of the disease in the area, e.g. Bilharziasis.

(iii) Epidemic = the occurance of cases of an illness clearly in excess of normal expectancy. This implies:

- Any disease outbreak
- No universally acceptable number of cases.
- May encompass any time period, from few hours to years.
- No specification of geographic extent.

(iv) Pandemic = world-wide epidemic (involving several countries)

(v) Exotic epidemic = epidemic occuring for the first time, or recurring after complete absence from the area

(vi) Sporadic = occassional or infrequent occurence of disease

b) With regard to time:

(i) Secular trend = change over a long period of time; years or decades.

(ii) Cyclic change = periodicity; annual (seasonal) e.g. diarrhea, or every several years e.g. measles

c) With regard to severity:

a	b	c	d	e
Inapparent	Mild	Moderate	Severe	Fetal

% of infection

(i) Sub-clinical = inapparent manifestations

(ii) Clinical = mild, moderate, severe or fatel

- Pathogenicity = $\frac{\text{Cases of disease}}{\text{\# infected}} = \frac{b + c + d + e}{a + b + c + d + e}$

- Virulence = $\frac{\text{Severe \& fetal cases}}{\text{all cases}} = \frac{d + e}{b + c + d + e}$

- Case fatality = $\frac{\text{Fetal cases}}{\text{all cases}} = \frac{e}{b + c + d + e}$

4. Selected Definitions & Concepts:

- **Periods of:** incubation, extrinsig incubation, communicability and generation:
  - Incubation period (IP) = period between entry of an agent into host and onset of first symptom or sign of the disease.
  - Extrinsic IP = period taken by the agent outside the human body until it becomes infective. Examples:
    - Inside a vector: e.g. Plasmodia take 12+ days in the Anopheline mosquito to complete its sexual cycles, then become infective.
    - In an intermediate host e.g. Bilharzia in snails takes weeks before cercaria emerge.
    - In inanimate reservoir as soil, e.g. Ascaris eggs take 14 days in soil to embryonate and become infective.
  - Period of communicability = period during which the host (man or animal) continues to be a source of infection to another host.
  - Generation period = period between entry of an agent into host and maximal communicability of that host.
- **Reservoir and Carier State:**
  - Reservoir = living organisms or inanimate matter in which an infectious agent normally lives and multiplies.
  - Carrier = an infected person who does not have apparent clinical disease, but is a potential source of infection to others. Carriers are of 4 types:

(i) In-apparent (asymptomatic) = person harbours the agent but with no clinical disease throughout, e.g. poliovirus, diphtheria.

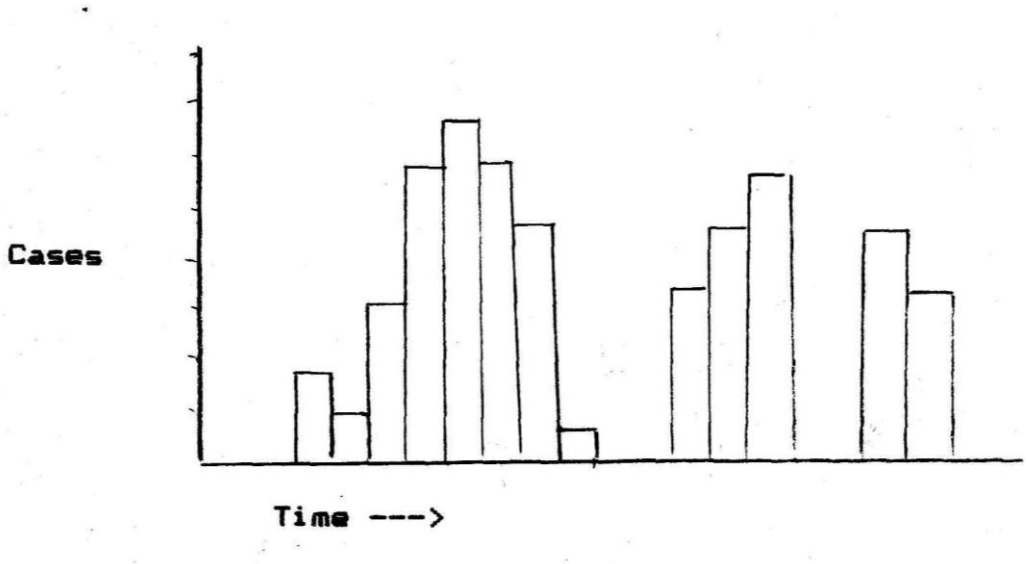
(ii) Incubatory = the carrier state preceeds manifest disease, e.g. measles

(iii) Convalescent = carrier state follows manifest disease, but pathogenic changes are not completely recovered e.g. diphtheria, hepatitis B

(iv) Chronic = carrier state persists for a long period after recovery e.g. S. typhosa. (post-convalescence)

- **Epidemic Curve :**

Plotting cases by time of onset



The Curve is useful in determining the median incubation period and number of cycles of propagation of infection over more than one IP.

- **Attack Rate:**

- Attack Rate = $\frac{\#\text{of index cases}}{\text{Pop .at risk}}$ during a limit period

- Secondary Attack Rate

$$= \frac{\#\text{ of cases who got the disease from an index case}}{\text{Pop .at risk exposed to the index case}}$$

- **Host Defence Mechanisms:**

a) General resistance of the host: as inherited by body constitution (anatomical or physiological), or extrinsic (aquired), e.g.
   - Intact skin and mucous membrances.
   - Sweat, tears, gastric acidity, sneezing, diarrhea ... etc.
   - WBC and reticuloendothelial system.
   - Good nutrition.
   - Good physical and mental health.

b) Specific = Immunity: resistance associated with possession of antibodies having a specific action on the microorganism of a particular infectious disease or on its toxins. Immunity is either:
   (i) Natural: either
      - Passive: congenital immunity from mother.
      - Active: after disease or subclinial infection.
   (ii) Artificial: either
      - Passive: by inoculation of specific protective antibodies or immune serum (gamma-globulin).
      - Active: by inoculation of antigen (live or killed), or toxiods or toxin-antitoxin mixture.

- **Herd Immunity** (immunity of a group or community) = the resistance of a group to invasion and spread of an infectious agent based on the immunity of a high proportion of the group members.
- **Virgin Pop.:** A pop. in which an organism has not been present for many years, if ever.

III. MODEL OF DISEASE CAUSATION

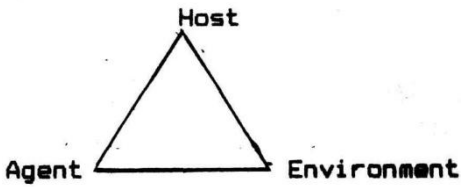
1. Model of Disease Multiple Causation:

- From the narrow medical view point, introduction of an organism into a community would be enough to explain the development of an outbreak.

Organism → Man → Disease

- It is true that the organism is the agent, because it must be present for disease development. However, from the epidemoilogic view point, the organism alone is not sufficient to account for the outbreak. Other factors (host & environmental) facilitate or enhance susceptibility to, and propagation of the disease. That is, for an outbreak to develop, more than one factor has to be present. This concept is referred to as "multiple causation or multifactorial etiology". This concept had led to the development of 3 models:

a) The epidemiologic triangle:

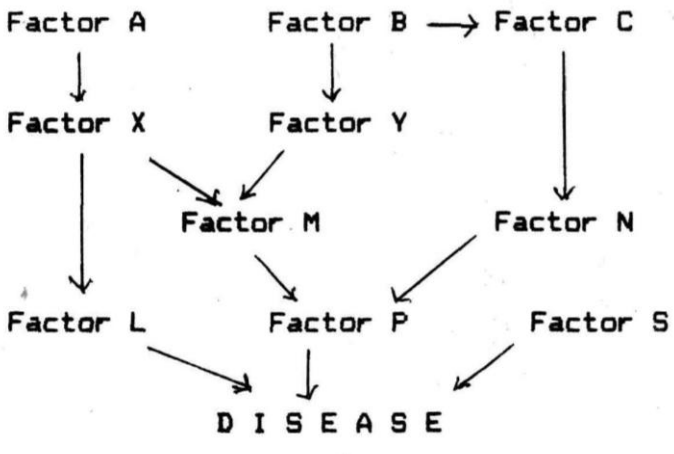


The model consists of 3 components: host, environment and agent, which interact to develop disease. A change in any of the components will affect the equilibrium to increase or decrease the frequency of the disease. This model particularly applies for infectious diseases, while the other two models which de-emphasizes the role of the agent, are more applicable to non-infectious diseases.

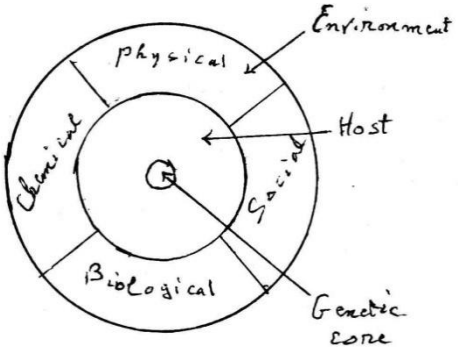
b) The web or network of causation:

The model implies that disease is developed as a result of "chains" of causation.

This model imples that cutting the chains at different points would interrupt the disease development, even without complete uderstanding of causal mechanisms.



c) The wheel model:



This model represents the host (man) as the focus, who has genetic make-up as its core, and is surrounded by the four environmental elements. The relative sizes of the wheel components vary from one disease to the other. In contrast to the previous model, the wheel model distinguishes the host from the environmental factors, thus more useful for epidemiologic analysis.

2. Epidemiologic Reasoning:

The calculation of morbidity and mortality indices help in identifying groups with high or low rates of a specific disease. Such descriptive data provide the first step in elucidating the causes (or risk factor) of the disease. The second step is an attempt to find WHY the disease is high or low in a particular group. Observation of differences in occurrence of the disease between pop. groups lead to the formulation of HYPOTHESIS i.e. testable proposition. This process is referred to as epidemiological reasoning which entails two steps:

a) Determination of statistical association between the disease and group characteristics.
b) Derivation of inferences from pattern of statistical associations.

3. Associations:

- Detection of causal associations is important to indicate key points at which a disease production (or propagation) can be interrupted. Differences in occurrence of a disease between pop. groups helps to determine statistical association. Not all associations, however, are causal. In order to concentrate attention to fruitful preventive measures, all possible explanations of the differences should be considered, before accepting any association as causal. Deciding if a factor is causally linked to a disease allows a chain of logic, by answering the following questions:

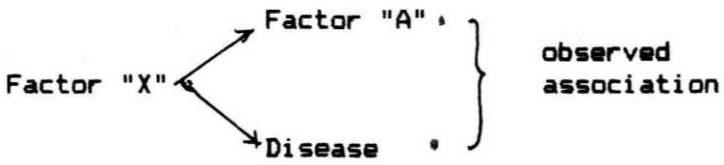
- Is the difference between groups statistically significant? If not significant, the problem may either be ignored or further studied on a larger sample. If statistical association exists, it may be positive or negative. It is positive if the observed proportion of individuals with both the factor and the disease is higher than expected; and is negative if the proportion is lower.
- Does the group (with high or low rate of disease) have any characteristics which might influence the rate, other than the one being studied? If there are evidences of the presence of such factors, analytical procedures can be applies to determine their effects and to neutralize them.

o The association may be artifactual or true. True associations may be indirect or direct.

a) Artifactual (spurious) association is a false association which can be due to chance, or to some bias in study methods. Bias might result from the interviewers attitude, from ability of the respondent to recall events or his/her desire to please the interviewer, from the way the interview questionnaire is constructed, or -from selection of the study group (e.g. hospital attendants).

b) True association:

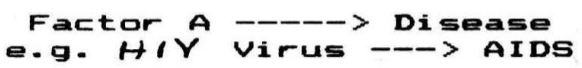
✓ Indirect association means that a factor and a disease are associated only because both are related to some common underlying condition.



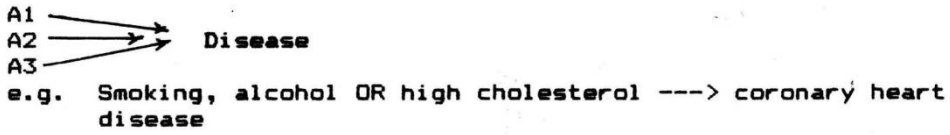
✓ The example of malaria is a prominent example, mal (bad) air (from which the name of the disease had been derived), was proved to have an indirect association with the disease.

✓ Direct (causal) association implies that the specific factor is the cause of the disease. There are 4 types of such association, displayed in the following diagrams.

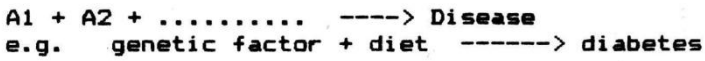
Necessary and sufficient:



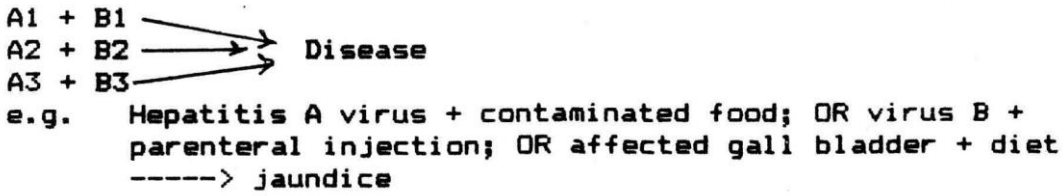
ii) Sufficient but not necessary:



iii) Necessary but not sufficient:



iv) Neither necessary nor sufficient:



4. Assessing Causal Association;

Causal association implies that change in one -factor is followed by a change in the other. However, there are certian criteria that have to be fulfilled before accepting a factor as the cause of a disease.

- The set of rules known as "Kock's postulates" requires 3 conditions to accuse an organism as the agent:

"... first, the organism is always found with the disease, in accord with the lesions and clinical stage observed; second, the organism is not found with any other disease; third, the organism, isolated from one who has the disease and cultured through several generations, reproduces the disease (in a susceptible experimental animal)…. Even where an infectious disease cannot be transmitted to animals, the "regular" and "exclusive" presence of the organism proves a causal relationship." (Quoted from Mausner & Bahn: p 100)

- At present, epidemiologists use the following set of criteria for judging whether a statistical association is causal or not:
  a) Strength of the association: i.e. a high relative risk.
  b) Dose-response relationship: i.e. the greater the dose of exposure, the greater the risk of the disease response.
  c) Temporal (i.e. time) sequence of the relationship: i.e. the exposure should precede the disease. However, in some conditions it might be difficult to document the sequence because of long latent periods.
  d) Consistency of the association: i.e. the findings are replicable, or the association persists under other circumstances
  e) Specificity of the association: i.e. the extent to which the "" occurrence of one factor can predict the occurrence of the other (will be discussed in section VI). This criterion is not essential.
  f) Biological plausibility; i.e. coherence with (fitting in) existing information.

EXERCISE

1. Indicate how the concept of multiple causation applies to the condition of tetanus.
2. Following is an (arbitrary) annual death rate/100,000 population from bronchopneumonia for selected cities:

Alexandria	15.0	Sohag	22.0
Saint Catherine	12.0	Ismaileya	25.0

Do these figures indicate a causal association between climate and death from bronchopneumonia? Why?

If no, what are other possible explanations?

IV. EPIDEHIOLQGIC APPROACH TO STUDY A PRDBELM

1. Scope of Epidemiology:

Epidemiology *is* the study of the distribution and determinants of disease and injuries in human population. Only after infectious disease epidemics had come under control, epidemiologic approach was applied to non-infectious diseases. This development was achieved by the use of a systematic approach to study disease and health problems; known as epidemiologic method.

2. Epidemiologic Method:

The epidemiologic approach to study a problem established long time ago, had laid the basis of scientific research. The epidemiologic method involves the following steps:

a) Initial observation in laboratory or clinical findings. Jenner was able to develop the first immunization program (vaccination against smallpox by cowpox) merely on the basis of observation, before the knowledge of the etiology.

b) Definition of disease or process by:
   i) Pathology
   ii) Common clinical characteristics
   iii) Specific etiological agent

c) Descriptive epidemiology: the study of amount and distribution of disease within a population (i.e. community diagnosis) by: person, place and time (i.e. who is affected? where and when do the cases occur?)

d) Developing an "Etiological Hypothesis" by applying analytical epidemiology i.e. the study of determinants of disease, or reasons for disease distribution; i.e. why the disease frequency is high (or low) in specific population groups? Such study include analysis of the association of disease with possible factors (agent, host and environment) in the natural history of the disease; and the pathogenic process of the disease in the community (i.e. means of spread) and its outcome.

e) Further refinement and testing of the etiological hypothesis, through:

i) Further manipulation of data; and/or

ii) Collection of additional information

f) Studying the impact of varying some factors under control, (an approach known as Experimental Epidemiology). Experimentation is usually carried out on laboratory animals, but rarely on volunteered human-beings. Results of experimental epidemiology may lead to modification of etiological factors, in order to control or prevent the disease in a population.

3. Investigation of Acute Outbreak

- The investigation of an epidemic is based on the epidemiologic method. Successful investigation requires:
  - Tedious collection of information in the field;
  - Careful analysis of data; and.
  - Intelligent interpretation of findings.

Investigation of an acute outbreak may be:

- Deductive: i.e. reasoning from previously proved situations; and/or.
- Inductive: i.e. reasoning from conclusions reached from analysis of particular facts.

- **The usual steps followed to:**

a. Define the problem (outbreak) by questioning:

- Is the diagnosis correct?
- Is the disease known?
- Are its causes understood?
- Have all cases come to attention?

b. Describe the outbreak by questioning:

- Who are affected? At what rate?
- When was the onset?
- Where are the cases located?
- What are the time place interactions? (pop. mobility or migration).

c. Examine the risk in subgroups of the affected population, by questioning:

- What are the risk factors?
- Which factor (variable) is suggestive of being the cause?

d. Develop hypotheses on the basis of:

- Existing knowledge (if any) of this disease.
- Analogy of disease of known etiology.

e. Test the hypotheses by:

- Further analysis of existing data.
- Collection of additional data.

Investigation of a food born outbreak by epidemiological approach. The following is an example of such approach:

- 75 persons had attended a party, over a period of a few hours 46 persons became ill with gastrointestinal symptoms, with an attack rate of 60%
- A list persons who attended the party, along with an indication of which foods each person had eaten and whether if he became ill or remained well was tabulated inthe following is an example:

No.	Age	Sex	Time of eating	Date & time of onset	State of health	Type of food			
						ham	coffee	cake	milk
1	11	Male	-	19 12 am	Well	✓		✓	
2	59	Female	8:00pm	19 12 am	Well		✓		✓
3	65	Female	6:00pm	19 12 am	Ill	✓		✓	
4	59	Female	6:30pm	19 12 am	Ill		✓		✓

From similar list construct an attack rate table for the attendees 75 persons as follow:

Type of food	Group A who ate specified food			Attack rate (%)	Group B who don`t ate specified food			Attack rate (%)
	ill	Not ill	Total		ill	Not ill	Total	
Ham	29	17	46	63	17	12	29	58.6
Vanilla	43	11	57	79.6	3	18	21	14.3
Chocolate	25	22	47	53.2	20	7	27	74.1
Coffee	4	2	6	66.7	42	27	69	60.9
Spwoch	26	17	43	60.5	20	12	32	62.5
Prato	23	14	37	62.2	23	14	37	62.5

Comparison of attack rates by ingestion of specific food show that only for vanilla ice cream was the attack rate substantially greater among those who ate the item than among those who did not (14.3%). Analysis by X^2 test revieled whether the difference is significant or not (79.6).

If more than one food appears to be suspicious (as chocolate ice cream) one can develop a cross reference table parallel to the analysis of matched pairs.

Cross reference table for vanilla and chocolate ice cream:

		Ate chocolate ice cream	**Didn`t ate chocolate ice cream**	**Total**
Ate vanilla ice cream	Ill/total	22/28	20/25	43/54
	% ill	78.6	80	79.6
Didn`t ate vanilla	Ill/total	3/14	0/2	3/21
	% ill	15.8	00	14.3
Total	Ill/total	25/47	20/27	46/75
	% ill	53.2	74.1	61.3

- This cross reference table indicate that who didn`t eat either vanilla or chocolate show 0/0% attack rate while those who ate vanilla ice cream whether consumed chocolate or not had identical attack rate 78.6% and 80% i.e. vanilla ice cream is the source.
- Once the source of contamination (either food or food handlers) appropriate control measures may be probable.

OUTLINE OF THE INVESTIGATION OF AN EPIDEMIC ***(Source: Epidemiology, An Introductory Text; Mausner & Bahns U.S. Saunder Company First edition, 1974).***

Preliminary Analysis

Verify the Diagnosis: Do clinical and laboratory studies to confirm the diagnosis.

Always consider whether initial reports are correct. For example, an outbreak of jaundice initially diagnosed as "leptospirosis" (a spiroehctal disease usually transmitted by water contaminated by the urine of infected animals) was found to be infectious hepatitis. The confirming tests indicated that one laboratory reagent was faulty. Investigation of a purported, epidemic of "gonorrhea" among the girls in a grade school revealed a "phantom epidemic" based on rumors **(Mausner and Gezon, 1967).**

It is necessary to establish-criteria for labelling persons as "cases." Depending on the type of problem being Investigated, the classification will be based on symptoms, laboratory results, or both.

Verify the Existence of an Epidemic: Attempt to compare the current incidence with past levels of the disease to determine whether an excessive number of cases have occurred.

Describe the Epidemic with Respect to Time, Place and Person: Plot the cases by time of onset (epidemic curve).

Plot the cases by location spot map).

Characterize persons by tabulating distribution of cases by age, sex, occupation, and other relevant attributes. The identification of "relevant" attributes may be a crucial step in the solution of the problem. For example, in the winter of 1960 to 1961 the New Jersey State Health Department became aware that an unexpectedly large proportion of the cases of hepatitis reported to them were occurring in adult males. This intelligence led eventually to identification of

contaminated clams taken from Raritan Bay as the vehicle of spread for these cases (Dougherty and Altman, 1962).

Formulate and Test Hypotheses: Identify type of epidemic common source vs. propagate.

Using above descriptive characteristics to define the population which has been at highest risk of acquiring the disease, consider possible source or sources from which disease may have been contracted. (compare ill population (cases) with well population (controls) with regard to exposure to the postulated source. Carry out statistical tests to determine probable source. When appropriate, attempt to confirm epidemiologic findings by laboratory tests (samples of blood or feces, samples of suspect food, and so on).

Possible further Investigation and Analysis

- **Search for Additional Cases:** Locate unrecognized or unreported cases by:
  1. Canvass of physicians or hospitals or both in the area to determine if they have seen other patients who might have the disease under investigation.
  2. Intensive investigation of asymptomatic persons or those with mild illness who may be contacts of cases. For example, in an investigation of an outbreak of hepatitis might do liver function tests (e.g., serum trans-aminase levels) to search for cases of anicteric hepatitis (i.e., non jaundiced), which ordinarily would not come to diagnosis.
- **Analyze the Data:** Assemble the results. Interpret findings.
- **Make a Decision about the Hypotheses Considered:** By the conclusion of the investigation all of the known facts should be consistent with one, and only one, hypothesis.

Report of the Investigation

At the termination of an investigation a report is usually prepared and submitted to the appropriate agency (or agencies). The report generally includes discussion of factors leading to the epidemic, evaluation of measures used for control, and recommendations for prevention of similar episodes in file future.

EXCERCISE

3. As a health officer of district "X", you received reports of 5 cases of typhoid - fever -from one village over a ten-day period.

   List the steps you would take to determine whether there has been a common source outbreak of the disease.

4. Over 150 persons were reported ill. The most common symptoms were diarrhea and cramps; a minority had nausea, vomiting and prostoration. Information collected revealed that the disease started 10-13 hours after eating at a wedding ceromony. Based on information about the specific foods eaten by all invitees, the attack rates were calculated (Table 1).

Table 1: Food-history Attack Rates

Food	No. of persons who ate				No. of persons who did NOT eat			
	Ill	Not ill	Tot.	%ill	Ill	Not ill	Tot.	%ill
1- Fried meat	97	36	133	72.9	2	23	25	8.0
2- Beans	77	28	105	73.3	22	31	53	41.5
3- Okra	59	39	98	60.2	40	20	60	66.7
4- Green salad	88	33	121	72.7	11	26	37	29.7
5- Fried potatoes	92	35	127	72.4	7	24	31	22.6
6- Rice	50	16	66	75.8	49	43	92	53.3
7- Dessert	22	14	36	61.1	77	45	122	63.1

   a) What features in such a table would incriminate a particular food as being responsible for the outbreak?

   b) Does the table suggest that only one food or more are responsible ? If the latter, what further information may be helpful in incriminating a specific food?

3. Further analysis of food-history of the previous outbreak revealed results in (Table 2).

Table 2: Food Cross-tabulation Attack Rates

		Ate salad	Did not eat salad	Total
Eat meat	Ill	88	9	97
	Not ill	33	3	36
	Total	121	12	133
	% ill	72.7	75.0	72.9
Did not eat meat	Ill	0	2	2
	Not ill	0	23	23
	Total	0	25	25
	% ill	0	8.0	8.0

a) What is the value of such analysis ?

b) What can you conclude from the table ?

V. MEASUREMENT OF COMMUNITY HEALTH

1- Introduction

- Assessment of the level of community health depends on measurement of morbidity (illness) including disability, of mortality (deaths) and of fertility (birth).
- Absolute numbers of events are of no value, unless related to specified population bases, for comparison. A rate is thus calculated to measure the frequency of an event in relation to a unit of population, along a specified time span.

Rate

- Nummerator = number of events
- Denominator = size of pop. unit at risk
- Period of observation: any duration, but usually one year
- Specified pop. unit

Morbidity and mortality rates are useful to:

- Study etiologic or risk factors, and thus can provide estimates of probability or risk of illness, disability or death.
- Tell the rate at which disease occurs or is present, thus help to determine the work load, rational planning of facilities and services, and monitoring control programs.
- Tell about quality of life, as reflected e.g. in identifying population segment affected, or level of disability.

2. Indices of Morbidity:

- There are 2 basic types: incidence and prevalence.

a. Incidence rates provide a measure of the rate at which people WITHOUT the disease DEVELOP the disease during a specified PERIOD of time i.e.

$$\text{Incidence rate} = \frac{\text{No. of NEW cases}}{\text{Pop. AT RISK}} \text{ over a period of time}$$

b. Prevalence rates measures the proportion of the people who HAVE the disease at a given point in time, i.e.:

Prevalence Rate = No. of EXISTING cases at a point in time.

Total population

- The prevalence rate referred to above is actually "point prevalence. There are 2 other measures of prevalence.

a. Period prevalence = No. of existing cases during a period

Average population

This measure is less commonly used.

b. Cummulative (- lifetime) prevalence:

= No. EVER ill at a point in time

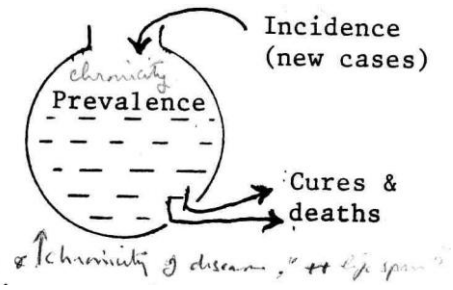
Total Pop.

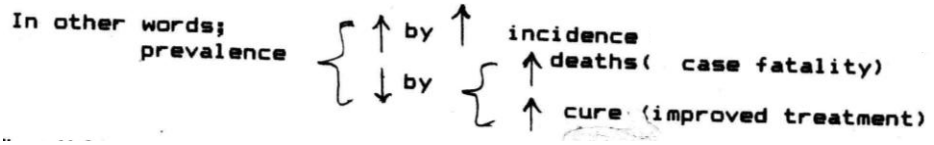
This index has little operational value in measuring morbidity, but the formula is commonly used in operational measurement of interventions such as contraceptive use or oral dehydration therapy use.

- Prevalence measures the residual of the illness, thus depends on 2 factors:-

- How many people have become ill in the past (i.e. previous incidence).
- The duration of the disease, which is determined by: degree of fatality and level of health services.

That is prevalence varies directly with incidence and duration; i.e. P = I.d





- The differences between incidence and prevalence are summarized in the following table.

	Incidence	Prevalence
- Rate: o Numerator: o Denominator: o Time frame:	Events (new cases) Pop. at risk One year	Statements (all cases) Total population. A point in time OR any period.
- Reflects factors which affect:	Development of the disease	Development and duration of the disease.
- Useful as a:	Direct indicator of risk of both acute & chronic disease.	Reflection of survival as determined by case fatality & medical care

Limitations of morbidity measurements are mainly:

a) Time of onset: the earliest definitive, objectively verifiable event that can be identified.

b) Period of observation is usually one year, but can be any length of time. The one year incidence does not reflect seasonal variations. In an epidemic, the incidence rate is generally referred to as an attack rate.

c) Specification of numerator: In certain diseases, more than one attack can occur to the same person during the stated time period, e.g. common cold or diarrhea. This gives rise to 2 types of incidence rates:

- No. of diarrhea attacks in one year

  Population at risk

- No. of PERSONS who developed diarrhea in one year

  Population at risk

The first rate gives the average number of attacks per person per year, i.e. the number of diarrhea episodes expected among the group in a year.

The second rate gives the proportion of persons who got ill i.e. the probability or risk that any person will develop diarrhea in on year.

d) Population at risk may not be readily available or difficult to determine. The population at risks is the susceptible population i.e. the population subjected to the disease minus those who have the disease or are immune against it.

3. Indices of Mortality:

- Mortality rates can be expressed in terms of a total population (crude or adjusted rates) or of a subgroup (specific rates).
- **Crude Death Rate (CDR):**

As with Crude Birth Rate (CBR), CDR is a summary rate based on the actual number of the event (deaths) in a total population over a given time period, usually one year.

$$CDR = \frac{\text{No. of deaths in one year}}{\text{Midyear (1/7) pop.}} \times 1000$$

CDR is affected by differences between population in age composition, since there are differences between age groups in risk of death. Nevertheless, it is commonly used because it is a summary rate that can be calculated from a minimum of information. (This notion also applies to CBR).

- **Specific Mortality Rates:**

These are mortality rates constructed for specific demographic Characteristic, or for a specific disease. The two commonly used specific rates; either singly or in combination; are: - Age specific death rate (ASDR) e.g. Infant Mortality Rate (IMR) or any age e.g. $ASDR_{25\text{-}35}$

- Cause specific death rate i.e. deaths -from a specific cause whether; single disease (e.g. coronary heart disease) or a category of diseases (e.g. cancer)

Specific rates provide details which help better understanding of epidemiologic aspects of disease and population dynamics. This is clearly illustrated by the U-shaped mortality curve by age.

- **Adjusted (or standerdized) Rates:**

Present one summary figure for a total population, but statistical procedures are carried out to "remove the effect" of differences in population composition. Age is the variable for which adjustment is commonly required because of its marked effect on morbidity and mortality. Adjustment for other variables e.g. sex, occupation ...etc

are less frequently required. There are 2 methods for holding constant the age composition of a population; direct and indirect.

- In the direct method, age-specific rates observed in *2* or more populations are applied to an arbitrary chosen population structure referred to as a "Standard" population (The combined populations can be used as the standard population). Multiplying the standard population by the age specific rates in each population yields the number of" expected" deaths in each, from which the "adjusted" rate is calculated.

As an example the following 2 tables compare the crude and adjusted mortality rates of population A & B.

Table 1: Comparison of death rates in 2 populations by age

	Age (year)	Population Prop. No.	Age = specific death rate (per 1000)	No. of deaths	CDR (per 1000)
Pop. A	< 15	0.3 1.500	2	3	
	15-44	0.4 2.000	6	12	
	45+	0.3 1.500	20	30	
		---		---	
	All ages	1.0 5.000		45	9.0
Pop. B	< 15	0.4 2.000	4	8	
	15-44	0.5 2.000	8	20	
	45+	0.1 500	24	12	
		---		---	
	All ages	1.0 5.000		40	8.0

Table 2: Comparison of adjusted death rates o-f the 2 population

Age (years)	Standard Pop. (A+B)	Population A			Population B		
		Age- sp. rates	Expected deaths	Adjusted DR	Age- sp. rates	Expected deaths	Adjusted DR
< 15	3.500	2	7		4	14	
15-44	4.500	6	27		8	36	
45+	2.000	20	40		24	48	
			---			---	
All ages	10.000		74	7.4		98	9.8

- The indirect method is applied in circumstances where small number of deaths in one group leads to unstable age-specific rates, or its age-specific rates may not be known. In this method, standedization is based on age-specific rates rather than age composition. A population of known age-specific rate's or the general population) is used as the "standard" population. Its age-specific rates are applied to the population of interest, e.g. a group of industrial workers exposed to a specific factor, to yield the number of "expected" deaths. Then the Standerdized Mortality Ratio (SMR) is calculated using the formula:

$$SMR = \frac{\text{Observed deaths}}{\text{Expected deaths}}$$

If the ratio is greater than 1, then the exposure factor is risky. If less than 1, the factor is protective. An example is displayed in the following tables.

<u>Table 1</u>: Deaths by age for the standard population and exposed group

Age years	Standard population			Exposed group		
	Pop. (1)	Deaths (2)	Age-sp. Rate/1000 (3)	Pop. (4)	Deaths (5)	Rate /1000
15-29	11.000	34	3.1	23	1	43.5
30-44	10.000	65	6.5	44	3	68.2
45-59	9.000	99	11.0	62	8	129.0
	-----	----		---	--	
All ages CDR	30.000	198	6.6	129	12	9.3

Table 2; Standardized Mortality Ratio

Age (years)	Deaths rates in stand. Pop. (1)	**Exposed population**			
		No. Pop. (2)	Expected Deaths (3)= 1×2	Observed Deaths (4)	SMR (5) = 4/3
15-29	3.1	23	0.1	1	
30-44	6.5	44	0.3	3	
45-59	11.0	62	0.7	8	
		---	---	--	
All ages			1.1	12	10.9

The SMR of 10.9 indicates that even after age-adjustment, the overall death rate is still high though the SMR is less than the ratio of crude death rates of the 2 pop. (93.0/6.6 = 14.1).

- The following table summarizes the advantages and disadvantages of the 3 types of mortality rates.

	Advantages	Disadvantages
Curde Rates CDR	○ Actual summary rates. ○ Readily calculable for international comparisons (widely used despite limitations)	○ Since population vary in composition (e.g., age), differences in crude rates are difficult to interpret
Specific Rates	○ Homogeneous subgroups. ○ Detailed rates useful for epidemiologic and public health purposes	○ Cumbersome to compare many subgroups of two or more populations
Adjusted Rates	○ Summary statements ○ Differences in composition of groups removed permitting unbiased comparison.	○ Hypothetical rates ○ Absolute magnitude dependent on standard population chosen. ○ Opposing trends in subgroups masked

4. Sources of Data:

a) The common sources of morbidity data are:

- Communicable disease notifications by hospitals, health units and private doctors.
- Absenteeism records in schools and industry.
- Pre-employment and periodic physical examinations in industry and schools.
- Case-finding programs: disease surveillance (e.g. cholera), contact control and food handlers examination.
- Morbidity surveys on population samples.

b) The common sources of mortality are:

- National Census ("de facto" = recording persons according to their location at time of enumeration; "de jure"- recording them according to their place of residence)
- Vital event registers.
- Community-based surveys.

5. Methodological Problems and Limitations:

a) Methodological problems related to difficulties in accurately defining:

- Time of onset.
- Period of observation.
- Population at risk

b) Reporting of notifiable diseases is often neglected.

c) Hospital data:

- Usually suffer selective bias, (limited to hospital care-seekers) & are usually limited to certain conditions.
- Have no pop. base to calculate incidence and prevalence.

d) Vital statistics: may suffer:

- Under-reporting particularly of stillbirths and neonatal deaths
- Misclassification of cause of death (underlying versus contributing)

e) Census data usually do not provide up-to-date information.

f) Surveys have the problems of:

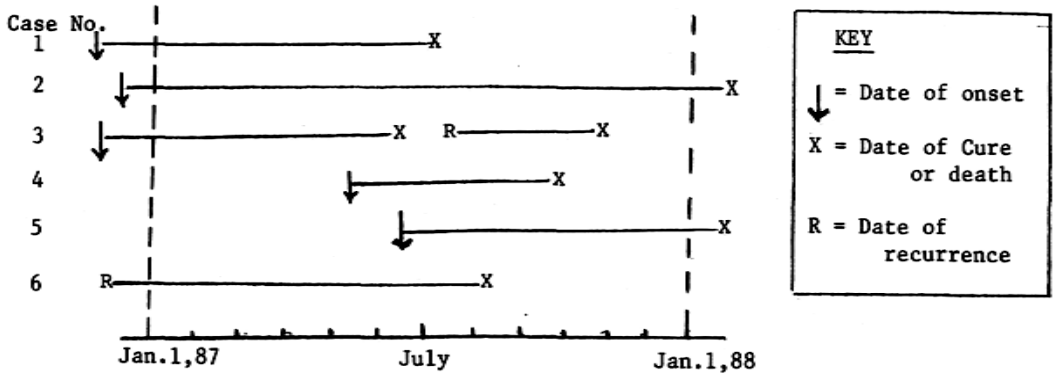
- Unawareness or difficulty to discover inapparent disease.
- Recall bias: inaccurate recall of a disease episode, or variation in perceptions of illness.
- Observer biases the interviewer may not ask/record, or may ask/record incorrectly.
- Selection bias, particularly with high non-response rates, or replacing household not at home by their neighbours.

g) Problems in comparing morbidity and mortality data:

- Population composition: age, sex ... etc.
- Differences in recognition/diagnosis of disease (differences in definition, of diagnostic criteria and in diagnostic methods).
- Inaccurate, or incomplete medical records, or tendency for over diagnosis.

PROBLEM EXERCICE

1. From the -figure, calculate the -following rates for a group of 300 persons.



b) Point prevalence on Jan. l, 1987.

c) Incidence rate for the year 1987.

d) Period prevalence for the year 1987.

2) The following table shows the population distribution and age-specific mortality rate for two districts.

Age years	**Dist. (A)**		**Dist. (B)**	
	Population	Age- sp. DR	Population	Age- sp. DR
0-14	6000	6.0	5400	5.0
15-29	4800	5.0	4200	4.8
30-44	4000	5.2	3000	5.2
45-59	3000	6.2	1600	6.5
60+	22	20.0	800	27.1
Total pop.	200.000		150.000	

Calculate for the two districts:

a. The curde death rates

b. The age-adjusted death rates and comment on the findings.

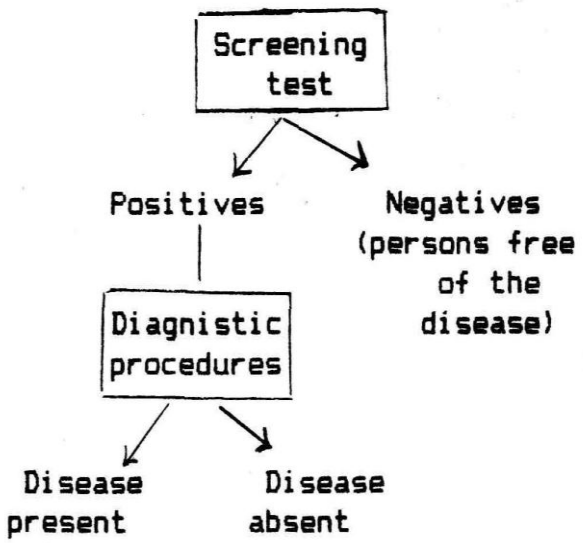
VI. EVALUATION OF DIAGNOSTIC AND SCREENING TESTS

1. Why Screening?

- The earlier the detection of the disease, the better is the prognosis. Early diagnosis is accomplished through 2 approaches:
  - Prompt attention to the earliest manifestations.
  - Attempts to detect disease in asymptomatic individuals.

  The first approach requires education of the public and care providers, so that they respond promptly. However, delays in response occur frequently. Hence, active detection of disease in apparently healthy individuals is needed in many conditions.

- This process, called screening or SURVIELLANCE. applies tests, examinations or other procedures to sort apparently healthy people who PROBABLY have the disease -from those who PROBABLY do not. Individuals who are positive to the screening test are thus subjected to thorough diagnostic procedures to sort those who HAVE the disease - from thos who DO NOT. As an example individuals positive for pulmonary Tbc on mass X-ray (or mini X-ray) are further examined clinically, by regular X-ray and bacteriologic examination of sputum.



- Since screening is applied to large groups, tests should be harmless, rapid, inexpensive and can be done by less qualified personnel.

2. Evaluation of screening tests:

- An ideal screening test would be 100 accurate. This, however, is not always the case. Three criteria are used to evaluate a screening test on the basis of comparing the test results with those derived from a definitive diagnostic procedure, independent of the screening test. These 3 criteria are:
  - Validity = Accuracy of results (correct result)
  - Reliability = Precision of results (exact measurement & repeatability)
  - Yield = The product (the amount of previously unknown disease that become diagnosed brought to treatment).

3. Validity: Has 2 components:

a) Sensitivity = ability to correctly identify those who have the disease.

b) Specificity = ability to correctly identify those who do NOT have the disease.

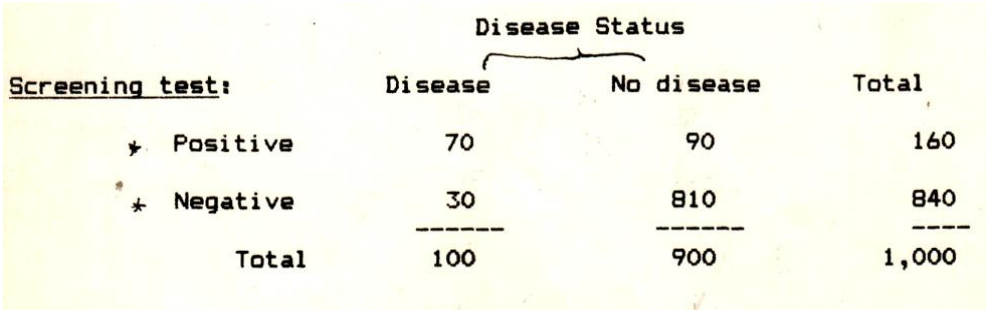
They are calculated as follows:

		Disease state by definitive diagnostic procedure	
		Disease	No disease
Results of Screening test	Positive	True positive (a)	False positive (b)
	Negative	False negative (c)	True negative (d)
	Total	(a + c)	(b + d)

- **Sensitivity (in percent) =** $\frac{a}{a+c} \times 100$
- **Specificity (in percent) =** $\frac{d}{b+d} \times 100$
- **False negatives (in percent) =** $\frac{c}{a+c} \times 100$
- **False positives (in percent) =** $\frac{b}{b+d} \times 100$
- **Systematic essor =** $\frac{a+b}{a+c}$

Example (1):

A definitive diagnostic produce among 1.000 pop. Showed that 100 have the disease and 900 do not. Comparison results of the screening test revealed that:



Screening test:	Disease Status: Disease	No disease	Total
Positive	70	90	160
Negative	30	810	840
Total	100	900	1,000

Then:

- Sensitivity = $\frac{70}{100} \times 100 = 70\%$
- Specificity = $\frac{810}{900} \times 100 = 90\%$
- False negatives = $\frac{30}{100} \times 100 = 30\%$
- False positives = $\frac{90}{900} \times 100 = 10\%$

Example (2):

Suppose that the screening test revealed that:

Disease status

Screening test:	Disease	No disease	Total
Positive	90	135	225
Negative	10	765	775
Total	100	900	1000

- Sensitivity = $\frac{90}{100} \times 100 = 90\%$
- Specifity = $\frac{765}{900} \times 100 = 85\%$

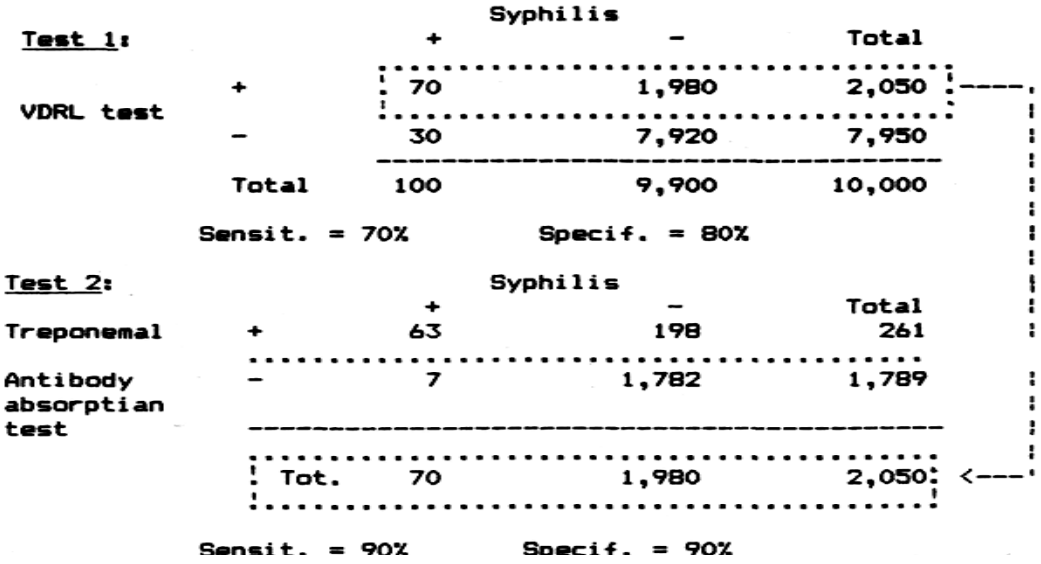
From the 2 examples, it is clear that:

- The percent of false negatives complements the percent sensitivity; and the percent false positives complements the percent specificity.
- Sensitivity and specificity are usually inversely related i.e. if sensitivity is increased, specificity gets down. This is attributable to the fact that as the screening test is improved to identify more cases among those who are diseased (i.e. better sensitivity), it will also give higher positive results among non-diseased (i.e. more false positive) and thus specificity gets poorer.

- **The decision to apply a screening test with good sensitivity and poor specificity, or one with opposite characteristics is determined by:**
  - The importance of mising a "possible" case.
  - The cost of diagnostic procedures of false positives.
  - The frequency of re-screening
  - The disease prevalence.
- **Two or more screening tests can be combined to improve sensitivity or specificity. There are 2 forms of combination:**

a) Tests in parallel: The person is labelled positive if he is positive in ANY of the tests, and subsequently negative if he is negative in ALL the test*. This approach improves sensitivity.

b) Tests in series] The person is considered positive if he is positive in ALL the tests. This approach which improves specificity is more commonly used. Cases positive to the first test are screened by the second (more specific) test.

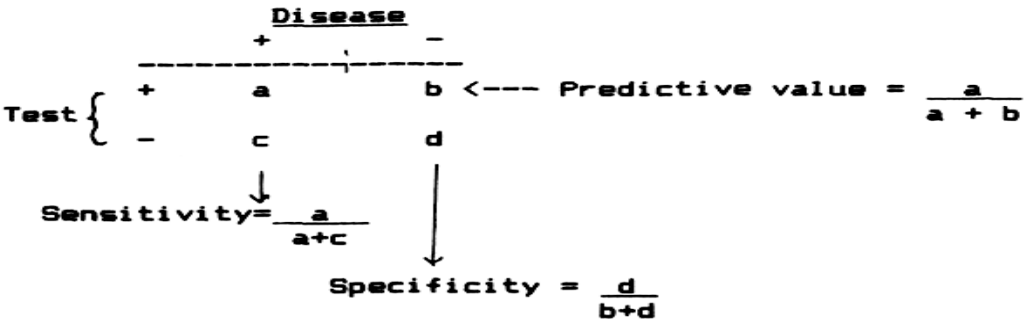


- The net sensitivity = $\frac{63}{100} \times 100 = 63\%$

- The net specifity = $\frac{7920+1782}{9900} \times 100 = 98\%$

That is with using both tests, there is a loss in net sensitivity and a gain in net specificity

- The <u>predictive value</u> of a test: is the likelihood that an individual with a positive test has the disease.



The predicative value is directly related to the disease prevalence as shown - from the -following example, assuming:

- Sensitivity = 90%

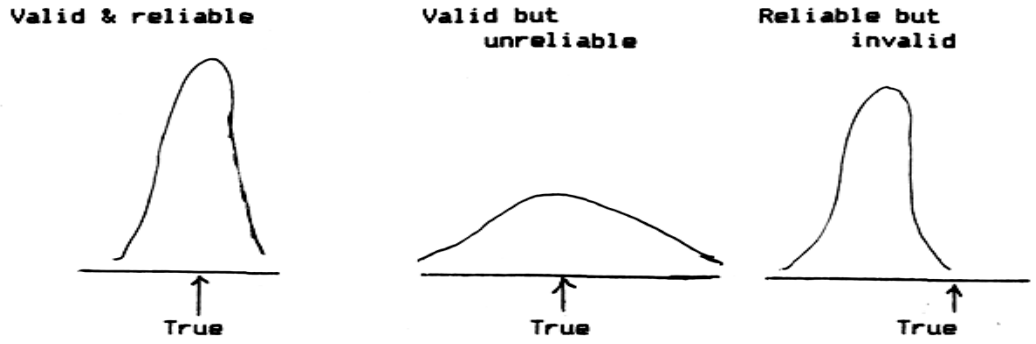
- Specificity = 95%

Disease prevalence	Test results	Disease status +	−	Total	Predicitive value	
1%	+	90	495	585	90 / 585 × 100 =	15.4%
	−	10	9,405	9,415		
	Tot.	100	9,900	10,000		
2%	+	180	490	670	180 / 670 × 100 =	26.9%
	−	20	9,310	9,330		
	Tot.	200	9,800	10,000		
5%	+	450	475	925	450 / 925 × 100 =	48.6%
	−	50	9,025	9,075		
	Tot.	500	9,500	10,000		

Such relationship of poor predictive value of a test if disease prevalence is low, implies that screening should be directed towards high prevalence groups, i.e. groups at high risk o-f the disease. For example, examining stool swabs for virbio for those groups who drink from polluted water sources rather than for those whose drinking water sources are free of the vibrio.

4. Reliability (Precision or repeatability):

A reliable screening test is one which gives consistent results when performed more than once on the same individual under the same conditions the following diagram illustrates the difference between validity and reliability.



Reliability is a measure of potential variations of the results. In general, there are 3 types of variations:

a) Intra-subject variation: due to biological variations of individuals screened, or variation of interviewees response.
b) Variation inherent in the method: depends on factors such as ability of reagents, method of testing, language of an interview questionnaire, or variability of the subject being measured (e.g. type of food varies daily).

c) Observer variation (= observer bias): is either:

i. Inter-observer variation in reading the result.

ii. Intra-observer variation i.e. variation of the reading by the same observer on separate occasions, e.g. early morning versus late at afternoon.

These variations can usually be reduced by:

- Careful standardization of procedures.
- Intensive training of observers or interviewers
- Periodic check on work.
- Using 2 or more observers making independent observation.

5. Yield:

It is the amount of previously unrecognized disease which is diagnosed and bought to treatment as a result of the screening test. The yield depends on:

- Sensitivity of the test: The yield is good, with high sensitivity.
- Prevalence of the unrecognized disease: The higher it is the higher will be the yield.
- Extent of previous screening: initial screening gives higher yield than repeat screening, as it detects cases that may have developed over years.
- Health behaviors: affect participation in the screening test and follow-up.
- The yield increases if the disease under study is perceived as serious, if action to abort the threat is expected, if the test is convenient and inexpensive, and if the individuals have positive attitudes towards observers and medical care.

6. Principles for Screening (surveillance) Programs:

For mass screening programs to be effective, the following requirements need to be considered:

a) The condition is an important health problem.

b) There should be a suitable and acceptable test.

c) There should be a recognizable latent stage.

d) There should be an acceptable treatment, and facilities for definitive diagnosis and treatment are available.
e) The cost of case-finding, diagnosis and treatment should be balanced in relation to costs if the test is not done.
f) Continuity of case-finding is administratively and financially feasible.

EXERCISE

A screening tact was done to 480 persons of whom 60 are known to have the disease. The test was found positive in 50 of the 60 people with the disease, and in 15 people who do not have the disease.

A) Calculate for the test its:

- Sensitivity
- Specificity
- % of false positives
- % of false negatives
- Predictive value.

B) Assume that sensitivity and specificity remained the same, but prevalence is 20%. What would be the predictive value?

VII. STUDY DESIGN

1. Objectives o-f Epidemiologic Studies:

a. Measurement of disease incidence and/or prevalence and outcome (prognosis).
b. Identification of etiologic/risk factors of diseases.
c. Measurement of outcome of exposure to risk factors.
d. Evaluation of therapeutic or preventive interventions.
e. Evaluation of new approaches to health care delivery.

2. Types of Study Approaches:

There are two basic approaches for testing hypotheses about disease etiology.

a. Experimental: measures the effects of the changes of a factor which is being under the control of the investigator. Examples measuring the effects of administering one versus two doses of a vaccine.
b. Observational: The investigator only observes the occurrence of disease among population groups who are already segregated according to exposure to some factors. Example: observing the occurrence of Bilhariasis among rural versus urban school children.

3. Types of Study Designs:

Study designs are classified into:

a. Cross-sectional.
b. Longitudinal:

i) Retrospective (case-control).

ii) Prospective (cohort).

Each design has its own advantages, disadvantages and uses.

4. Cross-Sectional Studies:

Are studies which examine different cohorts* at a given point in time. They thus provide a "snapshot" of experiences at that time, with regard to disease (or mortality) status, and etiologic factors in the study sample as a whole.

(*) A cohort is a group of persons who share a common attribute (feature or experience e.g. a birth cohort are person born in the same year or same period of years.

Advantages:

- Measure population sample characteristics.
- Determine disease magnitude (prevalence).
- Can study multiple factors and multiple diseases at the same time.

Disadvantages:

Show associations but do not indicate causal relationships.

Uses:

- Measurement of disease incidence/prevalence.
- If periodically repeated, show trends over time.

5. Retrospective Studies:

In a retrospective study, people diagnosed as having a disease (cases) are compared with persons who do not have the disease (controls); with regard to their past exposure to the possible etiologic factors of interest.

		FIRST: Select		
		Cases (Disease present)		Controls (Disease absent)
THEN: Measure past exposure	Were exposed	a		b
	were not exposed	c		d
	Totals	a + c		b + d

The proportions exposed among cases ($\frac{a}{a+c}$) and among controls ($\frac{a}{b+d}$) are calculated and compared for statistical differences by (Z or X^2).

Advantages:

- The number of subjects can be small.
- Results can be obtained relatively quickly.
- Low cost.

Disadvantages:

- Needed information on past exposure may be unavailable or inaccurately recorded in routine records.
- Biassed recall of events in the distant past.
- Problems in selecting cases and appropriate controls.
- Yields only an approximation of relative risk (Odds ratio), but can`t measure incidence (no pop. base).

Uses:

Particularly useful for etiologic study of rare diseases.

Methodological problems:

a. Problems to ascertain cases:

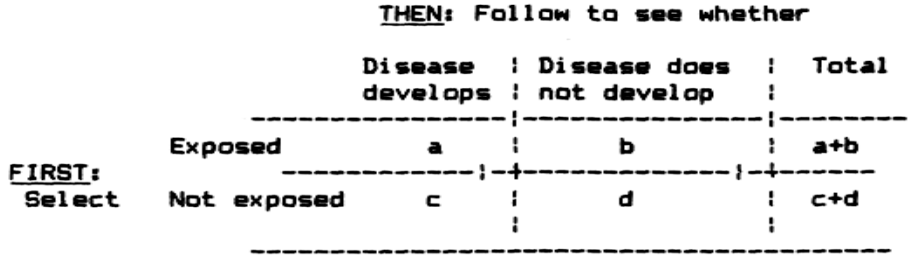
- Diagnostic criteria MUST be precise.
- Incident or prevalent cases must be already stated
- Source of cases must be defined, e.g. general population or hospital admissions.

b. Problems to select controls:

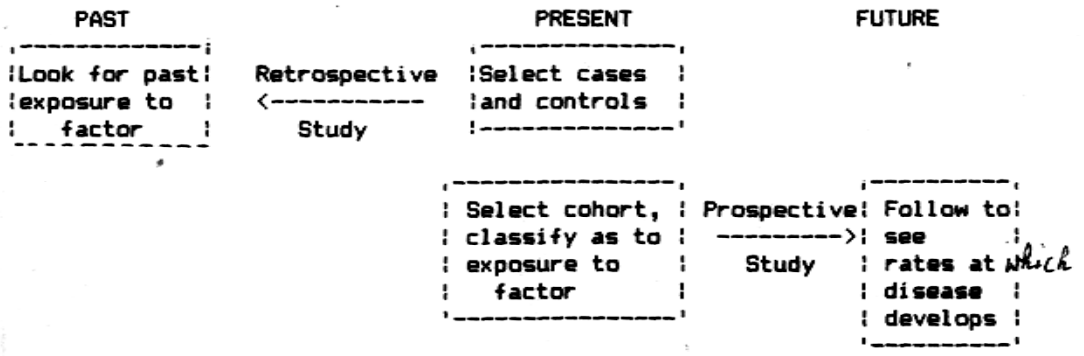
- Controls must be representative of the reference population.
- Source must be defined, and be appropriate to source of cases to allow comparability.
- Difficulties in matching or adjustment with cases.

6. Prospective Studies:

A prospective study starts with a group of people (a cohort) free of the disease under study, but who vary in exposure to a supposed risk factor. Both groups of the cohort are followed aver time to determine differences in the rates of disease development (or rate of death from the disease).



Thus prospective studies differ from retropsective studies in the way the study groups are selected. They also differ in the time sequence as shown in the following diagram.



Advantages:

- Lack of bias in ascertaining the exposure, since the cohort is classified as to the state of exposure before the disease develops.
- Permit calculation of incidence rates, thus both relative risk and attributable risk can be calculated.
- Permit observation of development of additional diseases as byproduct.

Disadvantages:

- Require large number of subjects.
- Long follow-up period.
- Attrition (i.e. loss of subjects from follow up) because of disinterest, migration, or death from other causes.
- Potential change of exposure status of subjects over time.
- Changes in diagnostic criteria and methods over time with advances in technology.
- Very costly.
- Potential loss of staff and/or funding.

Uses:

Particularly useful to study outcome when exposure is rare, but incidence among exposed is high (special exposure groups).

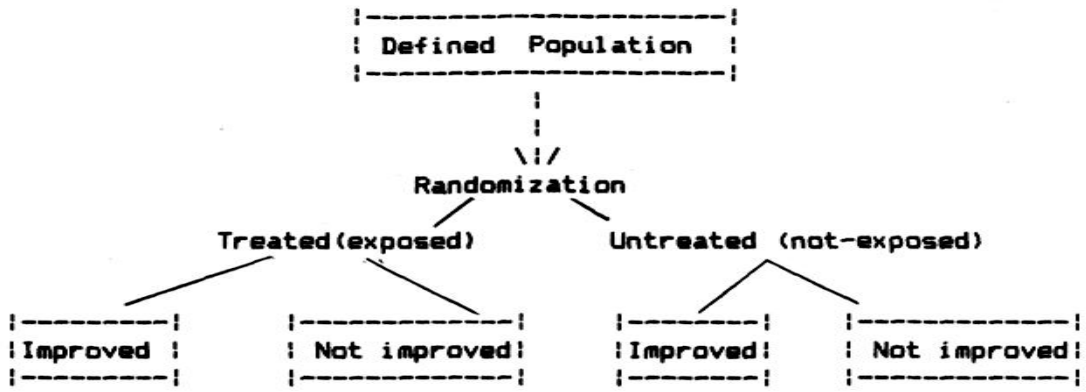
7. Clinical Trials:

The purpose of clinical trials is to compare a new agent, drug or vaccine with a traditional one with regard to its:

- Effectiveness.
- Safety (toxicity and side effects).
- Cost effectiveness.

• A clinical trial is a prospective study with two differences.

a) In a prospective study, subjects select themselves for exposure or non-exposure to the factor. In a clinical trial, the investigator randomly determines who will be exposed (treated) or not.



b) Masking (blinding) of:

- Subject → single blind.
- Data collectors.
- Data analysts.

} Double blind } Triple blind

Blindness can be achieved by using a similar shape, colour, taste or using a placebo.

- **Problems encountered include:**
  - Ethical issues.
  - Non-participation, attrition or non-compliance.
  - Correctly defining inclusion and exclusion criteria.
  - Precise measurement of outcomes.
  - Sample size.
  - Expenses.

8. Comparison of Study Designs:

	Cross-sectional	Retrospective	Prospective
a) Selection of persons:	- All persons; irrespective of disease & exposure status.	- Cases (with disease (a+c) - Controls (no disease) (b+d)	- Exposed (a+b) - Not exposed (c+d)
b) Outcome indices	- Disease prevalance.	-% exposed among: • cases= $\frac{a}{a+c}$ • Controls= $\frac{b}{b+d}$ - Odds ratio= $\frac{ad}{bc}$	- Incidence among: • Exposed= $\frac{a}{a+b}$ • Unexposed= $\frac{c}{c+d}$ - Relative risk= $\frac{a}{a+b} \div \frac{c}{c+d}$ - Attributable risk = $\frac{a}{a+b} - \frac{c}{c+d}$
c) Temporal relationship between exposure and disease	- Can not be established	- Sometimes hard to establish	- Easily established
d) Mutiple associations	- Mutiple diseases and mutiple factors .	- One disease & mutiple factors	- One factor & mutiple diseases
e) Requirements: - Pop. size - length of study - Cost	 Large Short Moderate	 Relatively small Relatively short Cheap	 Relatively large Long Expensive

9. Criteria for Choosing Study Method:

Any study method may be the most appropriate, depending on the factors: summrized in the following table.

Criteria	Cross-sectional	Retrospective	Prospective
a) Existing knowledge of the disease:	- Little information about disease incidence and nature of etiologic factors	- Little information about etiologic associations	- Causal[a] association known but not confirmed
b) Required information are:	- Not defined or specified	- Objective and available	- Subjective &/or unavailable
c) Level of disease incidence	- Unknown	- Disease is rare but exposure is common among diseased	- Exposure is rare but disease is frequent among exposed.
d) Latent parid		- Long	- Short

EXERCISE

1) Indicate the study design for the fallowing situations:

a. The district health administration received a weekly report showing that there were 9 cases of tetanus neonatorum. Investigations revealed that mothers of 8 cases had not received tetanus toxiod, and one mother had received only one shot two weeks be-fore delivery. Three infants were delivered at a rural hospital and 6 at home by daya. During the last month, the rural hospital had delivered 7 women, and conducted 4 minor surgeries of whom 2 got tetanus.

Daya (A) had delivered 10 women of whom 5 neonates had tetanus, and Daya (B) had delivered 13 women of whom one baby got the disease.

b. The Ministry of Health reported that during the last year, mortality among children under age three is high. The leading causes of death were: diarrhea, acute respiratory infections (ARI), and malnutrition. The mortality level by cause varied by region; diarrhea was higher in rural Uper Egypt, ARI in big cities and malnutrition in frontier governorates.

c. The Ministry of Health declared that the country is threatened by Cholera. Each health bureau was requested to take specimens from all water supplies and to watch the occurrence of the disease in its jurisdiction area.

2) Circle the correct answer:

a. Primary sampling of affected and non-affected groups are used in:

1. Prospective studies.
2. Retrospective studies.
3. Cross-sectional studies.
4. All the above
5. None of the above

b. Disease incidence can be directly calculated by:

1. Prospective studies only.
2. Retrospective studies only.
3. Both.
4. Neither.

c. Which of the following is NOT an advantage of a prospective study?

1. Precise measurement of effect of exposure is possible.
2. Usually more cheaper than a restrospective study.
3. Recall bias is minimized than in a retrospective study.
4. Many disease outcomes can be studies simultaneously.

3) The following table gives (hypothetical) annual age-specific mortalily rates/ 10000 children from measles during the first 5 years of age

Year of Death	**Age at death**			**Fourth**	**Fifth**
	First	**Second**	**Third**		
1976	1.3	1.5	1.1	0.9	0.8
1977	2. 1	2.4	3.0	1.8	2.0
1978	1.3	2.7	2.0	2. 1	1.5
1979	0.9	1.9	2.2	2.1	1.3
1980	0.7	0.9	0.5	0.2	0. 1

The age-specific mortality rates for the cohort born in 1976 are:

1.	1.3	1.5	1.1	0.9	0.8
2.	1.3	2. 1	1.3	0.9	0.7
3.	1.3	2.4	2.0	1.2	0. 1

VIII. MEASURING RISK IN EPIDEMIOLOBIC STUDIES

1. Determination of Risk Associated with an Exposure:

Analytic studies are designed to determine the extent of the disease occurence, whether there is an association between exposure to a factor and development of a disease, and how strong is it? Such questions can be answered by calculating the following risk indices:

a) Direct (absolute) risk (incidence rate).
b) Relative risk.
c) Odds ratio.
d) Attributable risk.

The following example serves to explain the concept and method of calculation of each.

Occurence of diarrhea among infants below 6 months of age by type of feeding:

Type of feeding	**Diarrhea**		
	+	**-**	**Total**
Bottle	150 (a)	90 (b)	240
Breast	28 (c)	622 (d)	650
Total	178	712	890

2. Direct Risk:

Direct or absolute risk is the <u>incidence or attack rate</u> of the disease. It can be calculated for either the:

- Exposed group = $\frac{a}{a+b} = \frac{150}{240} \times 100 = 62.5\%$.
- Non-exposed group = $\frac{c}{c+d} = \frac{28}{650} \times 100 = 4.3\%$
- Total group = $\frac{a+c}{a+b+c+d} = \frac{178}{890} \times 100 = 20.0\%$

The rate of 20% reflects the overall diarrhea incidence rate among infants below 6 months. The other two attack rates indicate that bottle-feeding is a risk factor for developing diarrhea, compared to breast feeding.

3. Relative Risk (RR):

The relative risk measures the strength of the association and is expressed as a ratio.

$$RR = \frac{\text{incidence among exposed}}{\text{" Nonexposed}} = \left\{\frac{a}{a+b}\right\} \div \left\{\frac{c}{c+d}\right\}$$

An RR of 1 (numerator = denomiator) indicates that there is no association. An RR greater than 1 indicates that exposed individuals are at greater risk of developing the disease than are the non-exposed. An RR less than 1 indicates that the factor is protective. In the example above:

R R = incidence among bottle-feeders = 62.5 = 14.5

" breast-feeders 4.3

i.e. bottle-feeding is 14.5 times as risky to develop diarrhea than breast-feeding. In other words, breast-feeding is 14.5 times protective against the disease compared to bottle-feeding.

The RR can be easily calculated from prospective studies. It can measure the relative risk of more than one exposure as shown from the following example:

Relationship between serum cholestrol level and risk of coronary heart disease by age and sex.

Serum Cholesterol	Males		Females	
	Age		Age	
Mgm %	30 - 49	50+	30 - 49	50+
	Incidence Rates/1,000			
< 190	38.2	105.7	11.1	75.2
190 - 239	84.4	196.5	16.1	91.8
240+	157.5	267.8	50.4	121.5
Relative Risk using males 30 - 49 years with chololesterol < 190 as reference:				
	1.0	2.8	0.3	2.0
	2.2	5.1	0.4	2.4
	4.1	7.0	1.3	3.2

4. The Odds Ratio (OR):

In a prospective study, the RR can be calculated directly. In a retrospective study we do not know the incidence in either the exposed or the non-exposed group. Hence we can not calculate the RR directly. In such case we can obtain a good estimate of RR by calculating the odds ratio, given 3 assumptions:

a) The incidence of the disease is low.
b) The cases are representatives of all cases with regard to exposure.
c) Control's are representative of the reference population with regard to exposure.

In a prospective study:

$$RR = \left(\frac{a}{a+b}\right) - \left(\frac{c}{c+d}\right)$$

If incidence is low, then (a) contributes little to (a+b), and (c) contributes little to (c+d) , i.e. (b) is a close approximation of (a+b) and (d) is approximation of (c+d). So excluding (a) and (c) from the denominators result in:

$$\frac{a}{a+b} - \frac{c}{c+d} \approx \frac{a}{b} \div \frac{c}{d} = \frac{ad}{bc} = "OR"$$

That is OR known as the cross products ratio is calculated by multiplying the diagonals of the 2×2 table. It should be noted that the "OR" does not give good estimate for RR if the above 3 assumptions are not fulfilled, as is the case with the feeding/diarrhea example:

$$OR = \frac{ad}{bc} = \frac{150 \times 622}{28 \times 90} = 37.0$$

5. Attributable Risk (AR):

Not all of the disease incidence is due to the exposure, since some non-exposed individuals develop the disease. Attributable Risk (AR) is the magnitude or proportion of disease excess risk which can be attributed to the exposure under study, "and subsequenctly a measure of the magnitude of the potential impact of its

elemination. It may be presented in absolute or proportional expression. It can be calculated for the exposed group or for the total population.

a) AR for the Exposed Group:

- Disease incidence in non-exposed group (N) = incidence not due to the esposure (background incidence);
- Incidence in exposed group (E) = background incidence + incidence due to the exposure.
- Therefore; the excess incidence in the exposed group which is attributable to the exposure: = (Incidence in exposed group) - (Incidence in non-exposed group)

i.e. AR for exposed group = E - N

and the proportion of total incidence in the exposed group attributable to the exposure

$$= \frac{\text{(Incidence in exposed group) - (Incidence in non-exposed group)}}{\text{Incidence in exposed group}}$$

i.e. Proportion AR for exposed group = $\frac{E-N}{E}$

EXAMPLE; A prospective study of smoking & coronary heart disease (CHD):

THEN follow-up to see how many developed or not developed (CHD)

First select:		Developed CHD	Do not developed CHD	Total
	Healthy somekers healthy non-smokers	84 87	2.916 4.913	3.000 5.000
	Total	171	7.829	8.000

Incidence in exposed group = $\frac{84}{3.000} \times 1000 = 28.0/1000/\text{year}$

Incidence in non-exposed group = $\frac{87}{5.000} \times 1000 = 17.4/1000/\text{year}$

i) AR in the exposed group = 28.0 - 17.4 = 10.6

ii) Proportion AR = $\frac{28.0-17.4}{28.0} = \frac{16.6}{28.0} = 0.379$ or 37.9

b) AR for the Total Population;

It is the proportion of disease incidence in a total pop, which can be attributed to the exposure. It is a valuable concept for the public health worker, because it estimates the proportional reduction in disease incidence in the total population if the exposrue is prevented by a public health intervention. By the same talk AR for the total pop.

= (Incidence in tot, pop.) - (Incidence in non-exposed group).

So, to calculate AR for the total pop., one must know either:

- Incidence in the total pop.; OR.
- Incidence among exposed and the proportion of the total pop. who are exposed.

EXAMPLE;

Using the previous example, and assuming that another study showed that the proportion of somkers in the total population is 40% (and therfore the proportion of non-smokers is 60%), then the incidence in the total population =

$$(28.0)\ (0.40) + (17.4)\ (.60) = 21.6/1000/\text{year}$$

Thus AR = 21.6 - 17.4 = 4.2/1000/year;

and the pop. AR proportion = $\frac{21.6-17.4}{21.6}$ = 0.194 or 19.4%

EXERCISE

Results of a study on infant mortality -from measles and from diarrhea! diseases for rural and urban are shown in the foil owing table. It was estimated that 44% of the total pop. are urban.

Exposure	Annual Infant Death Rates/IB.BBB category	
	Measles	Diarrheal Diseases
Urban	25	48B
Rural	IB	32B

1. Calculate for each disease
    a) The relative risk
    b) The exposed group AR
    c) The exposed group AR proportion
    d) The total population AR
    e) The population AR proportion
2. Comment on findings.

IX. HANDLING CONFOUNDING VARIABLES

1. Confounding Variables:

In order to obtain correct conclusions when comparing two groups (or populations), the groups ought to be as identical as possible with regard to their characteristics. However, in reality, this is not the case. As disease development (or death) is affected by multiple factors (multiple causation), the comparison of the 2 groups with regard to a specific factor will be distorted by the effects of other factors/characteristics. In this case, those other factors are referred to as confounding variables. Hence, there is a need to identify potentially confounding variables at the outset of any study. Their effects could be eliminated by fixing those variables among cases and controls. There are two approaches to handle the problem of confounding:

- In designing and carrying out the study by matching the controls to the cases.
- In the data analysis by stratification or adjustment.

2. Matching:

Matching means that controls should be as identical as cases with regard to all known factors (variables) except the one (or more) under study. Potential variables are related to:

- Person: age, sex, race, marital status, education, occupation, income, social class, family size ...etc.
- Place: urban, rural or semi-urban residence, geographic location, environmental factors ... etc.
- Time: year, season or may be time of the day. Matching may be for:

a) The whole group i.e. the characteristics of the control group are similar to those of the study group, except for the variable under study.

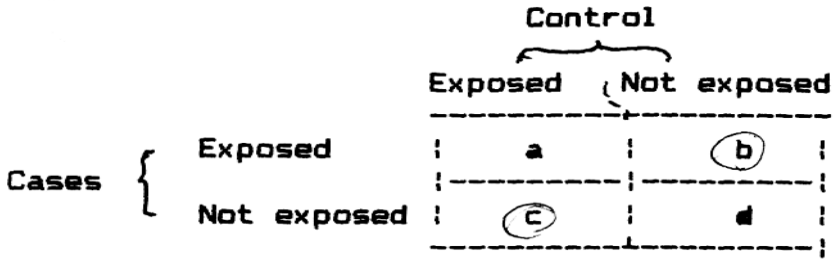
b) Individuals e.g. matched pairs (matched triplets ...) i.e. for each individual case, there should be a comparable control individual. Individual matching is difficult, particularly in large sample studies. Individual control is usually selected from the immediate living circle of the case, e.g. spouce, sibling,

relative or neighbour. By nature, such selection implies that the case and control are similar, but not identical.

3. Handling Confounding Problem in Data Analysis:

During the data analysis, the problem of confounding can be overcome by statistical procedures, such as stratification and adjustment.

- Stratification refers to the breakdown of data presentation by stratum, category or group e.g. low versus medium versus high income, urban versus rural, age 0-4, 5-9 ... etc. Such stratification of each of the study and control groups helps to estimate and compare the risk for each category or stratum.
- In matched pairs, results are analyzed by pairs. Four types of case—control pairs are presented as shown in the diagram:



(a) Pairs in which both case and control were exposed.

(b) Pairs in which case was exposed but control was not.

(c) Pairs in which control was exposed but case was not.

(d) Pairs in which neither case nor control were exposed.

The two types of pairs (a,d) are called concordant pairs, the other two types (b,c) are called discordant pairs. Unlike other 2x2 tables, the number in each cell represents case-control pairs but not individual subjects. The subsequently, estimation of relative risk (in terms of odds ratio) is based on the discordant pairs (b & c) only.

ODDS RATIO (matched pairs) = $\frac{b}{c}$

EXAMPLE: Assume a retrospective study on 10 cases and 10 controls revealed the following results (E= and exposed individual and N = an individual not exposed):

Unmatched Study

Cases	Controls
E	N
E	E
N	N
E	N
N	E
N	N
E	N
E	E
E	N
N	N

Total = 10 cases & 10 controls

Matched Study

Cases		Controls
E	<------>	N
E	<------>	E
N	<------>	N
E	<------>	N
N	<------>	E
N	<------>	N
E	<------>	N
E	<------>	E
E	<------>	N
N	<------>	N

Total = 10 **pairs**

	Cases	Controls
Exposed	6	3
Not exposed	4	7

$$\text{Odds ratio} = \frac{ad}{bc} = \frac{6 \times 7}{3 \times 4} = 3.5$$

		Controls: Exp.	Controls: Not exp.
Cases	Exp.	2	4
	Not Exp.	1	3

$$\text{Odds ratio} = \frac{b}{c} = \frac{4}{1} = 4$$

- Adjustment is the use of statistical procedures to "remove the effect" of differences of composition of the study and control groups to yield standardized rates. Adjustment is commonly done for age, but it may be necessary far other variables. An examples of adjustment for age, using both the direct and indirect methods was discussed in Section" V" (Adjusted death rates).

4. Driving Causal Inferences:

The purpose of handling confounding variables is to ascertain the type of association of the exposure factor and the disease, is it spurious or true? If true, is it indirect or causal? There are four approaches to study causes of human disease:

a) Using animal model; the problems with this approach are: no model exists (animals are not susceptile to all human diseases), and if the model exists, results may not be generalized to other species.
b) In-vitro experiments: The probelm with this approach is that the in-vitro interactions may be modified in-vivo.
c) Clinical studies on human subjects: Such approach is generally not ethical, hence it is rarely used.
d) Epidemioloqic studies; Cross-sectional, retrospective, prospective and clinical trials (see sections IV and VII).