GOALS of Lectures Sept 03-06.
- Learn nature and purposes of epidemiology
- Understand measures used in epidemiology
- Recognize different epidemiologic designs
- Realize their strengths and weaknesses
- Understand play of "chance" [random error]

TEXTBOOK

Lecture September 03
- Nature and Purposes of epidemiology [Ch1]
- Measures used in epidemiology [Ch 4]
- Experimental Studies [Ch 7]

CLINICAL MEDICINE
- DIAGNOSIS
- ETIOGNOSIS
- PROGNOSIS

PUBLIC HEALTH
- SURVEILLANCE
- PROTECTION
- PREVENTION

Symptoms/ Complaints
- TREATMENT
  - Benefits?
  - Risks?

Asymptomatic
- RISK MODIFICATION
- CASE-FINDING

Epidemiology used to identify / quantify risks and benefits and to guide decisions, actions and policies.

EPIDEMIOLOGY: DEFINITIONS
- (OLD) That branch of medical science which treats of epidemics (OED)
- a branch of medical science that deals with the incidence, distribution, and control of disease in a population (Merriam-Webster)
- the sum of the factors controlling the presence or absence of a disease or pathogen (Merriam-Webster)
- Epidemiology may be viewed as based on two fundamental assumptions: human disease
  - does not occur at random,
  - has causal and preventive factors that can be identified through systematic investigation of different populations or subgroups of individuals within a population in different places or at different times

This leads directly to a useful and comprehensive definition of epidemiology:
"the study of the distribution and determinants of disease frequency in human populations" [MacMahon and Pugh, 1970].

- measurement of disease frequency:
  Availability of data is a prerequisite for any systematic investigation of patterns of disease occurrence.
  - distribution of disease (who/where/when?) essential to describe patterns of disease as well as to formulate hypotheses concerning possible causal or preventive factors.
  - knowledge of frequency and distribution of disease is necessary to test epidemiologic hypotheses (determinants)

EPIDEMIOLOGY: MEASURES [Ch 4]
"NEW CASES": Incidence [see 2 types below]
"STATES": Prevalence
(event = transition from one state to another)

Fletcher (p77) calls it "incidence"
EPIDEMIOLOGY: MEASURES...

PREVALENCE (proportion, % etc.)
Num.: # EXISTING CASES (●)
Denom: # PERSONS (● + ○)

* "Time" can be a fixed Calendar Time (same for all) or fixed relative to some other 'clock' that starts at different calendar time for each person e.g. 3rd day post-surgery

"Period Prevalence": cases at some point during a specific period of time

A Point in Time*

See Table 4.1 (p 79) of Fletcher et al.

Other Applications

Concept of Prevalence also used for measuring frequency of behaviours, characteristics, states, etc.


Prevalence is central to DIAGNOSIS (see p 88)

Concept of Incidence can also be used for other desirable and undesirable life events and transitions (graduation, marriage, pregnancy, bankruptcy, promotion, ...)

<table>
<thead>
<tr>
<th>Rate</th>
<th>Type</th>
<th>Numerator</th>
<th>Denominator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity</td>
<td>Incidence</td>
<td>New cases of non-fatal disease</td>
<td>Total popln. at risk</td>
</tr>
<tr>
<td>Mortality</td>
<td>Incidence</td>
<td>Number of deaths from a disease (or all causes)</td>
<td>Total popln.</td>
</tr>
<tr>
<td>Case-Fatality</td>
<td>Incidence</td>
<td>Number of deaths from a disease</td>
<td>Number of cases of that disease</td>
</tr>
<tr>
<td>Attack</td>
<td>Incidence</td>
<td>Number of cases of a disease</td>
<td>Total popln. at risk, for a limited period of observation</td>
</tr>
</tbody>
</table>

Table Special types of incidence and prevalence measures (from Hennekens and Buring, p62)

Incidence, Prevalence and Duration
(see Fletcher p 84-85)

Prevalence depends on incidence rate and duration of disease from onset to termination.

- e.g. low inc. + long durn. -> high prevalence
- adult onset diabetes?
- AIDS?
- common cold?

Changes in prevalence over time

- change in incidence rates?
- duration?
- both?

#hospital beds in new MUHC mega-hospital?

In steady state..

Prevalence

\[ \text{Prevalence} = \text{Incidence rate} \times \text{average duration} \]

E.g.

Beds occupied

\[ \text{Beds occupied} = \text{Admissions/day} \times \text{average L.O.S.} \]

[Csizmadi also measured rate of starting HRT (an "incidence" measure)]
Experimental Studies
[from Rothman & Greenland, pages 68-71]

"Epidemiologic study types have their roots in the concepts of scientific experimentation. When epidemiologic experiments are feasible, their design is guided by principles that reduce variation by extraneous factors in comparison with the study factors. They include:

- **clinical trials** - patients as subjects
- **field trials** - interventions assigned to individual community members (i.e. to well "subjects")
- **community intervention trials** - interventions assigned to communities or other 'clusters' such as army units, schools, hospitals, families, physician practices.

In an experiment, those who are exposed to the agent or putative cause are exposed only because the investigator has assigned the exposure to the subject. Furthermore, the reason for assigning the specific exposure to the subject must be simply the pursuit of the study protocol. [i.e. to learn]

Because the goals of the study rather than the subject's needs determine the exposure assignment, ethical constraints limit the circumstances in which epidemiologic experiments are feasible. Experiments are ethically permissible only when adherence to the scientific protocol does not conflict with the subject's best interests. Specifically, there should be reasonable assurance that no participating subject could be treated better than the two or more treatment possibilities that the protocol provides. From this requirement comes the obvious constraint that any exposures or treatments given to subjects should be limited to potential preventives of disease or disease consequences. This limitation alone confines most etiologic research (i.e. on unintended effects) to the nonexperimental variety. [intended effects difficult to study non-experimentally]

Randomized Controlled Trials
(Fletcher, Ch 7, 138-55)

**NOTES:**

- Fletcher uses the term 'clinical trial' the way Rothman and Greenland use the term 'experimental study'.
- Figure 7.1 shows a "parallel arms' or 'between-subjects' comparison. In some situations (e.g. if disease or target of treatment is 'reversible', treatment course is reasonably short, and carryover of treatment effects can be avoided, -- see 2nd paragraph of p 155), a "serial" approach may be possible.
- In a 'within-subject' design, each subject receives each of the 'treatments' in random order (i.e. 'crosses-over' from one to other, one or more times). However, the greater statistical efficiency (in terms of the smaller number of subjects required) is offset by the fact that the duration in the trial for each patient is longer, the effects may not have washed out, the disease severity may have changed for other reasons, etc.

- **SAMPLING** (p 139, and Figure 7.2)
  The issue in this section is not so much 'sampling' as it is selectivity.

- **DIFFERENCES AFTER RANDOMIZATION**
  The two subsections Compliance and Cointerventions deal with key issues.

  The flawed practice of comparing ultimate outcomes (e.g. survival) in "responders" and "non-responders" following cancer treatment was driven from the literature in the early 1970's. Most other medical specialties and sub-specialties have since followed suit.

- **BLINDING**
  - This is another very important issue.
  - The authors are wise to advise "simply describe what was done by way of 'blinding' or 'masking". Textbooks and authors are indeed often ambiguous.

  Another level of blinding that is just beginning to be practiced is blinding of the statisticians and investigators in the statistical analysis itself.

- **SUMMARY MEASURES OF TREATMENT EFFECTS** (p150)
  The number required to treat' is becoming more widely appreciated and reported. If the absolute difference in outcomes rates is small, the large number of patients required to treat (i.e. to produce a benefit for 1 patient) will be offset by the large expense of treatment, and by the side-effects of treatment. Thus, absolute, rather than relative, differences are key for cost-effectiveness analysis.

- **MANAGEMENT VS EXPLANATORY EFFECTIVENESS vs. EFFICACY** (p151)
  These concepts are closely linked.

  The term 'intention to treat analysis' is now widely used.

  Efficacy studies are best done by restriction (i.e. before randomization), since trying to do so after randomization is quite difficult. The US Physicians Study (see bottom of p153) used a 'run-in' period and restricted the entry into the randomized study to those who were compliant.

- **SUBGROUPS** (p 152-154)
  The example of the 'second danger' concerns 'other outcomes', not subgroups.
EXPERIMENTAL STUDIES: EXAMPLES**


The largest and most expensive medical experiment in history was carried out in 1954. Well over a million young children participated, and the immediate direct costs were over 5 million dollars. The experiment was carried out to assess the effectiveness, if any, of the Salk vaccine as a protection against paralysis or death from poliomyelitis. The study was elaborate in many respects, most prominently in the use of placebo controls (children who were inoculated with simple salt solution) assigned at random (that is, by a carefully applied chance process that gave each volunteer an equal probability of getting vaccine or salt solution) and subjected to a double-blind evaluation (that is, an arrangement under which neither the children nor the physicians who evaluated their subsequent state of health knew who had been given vaccine and who got the salt solution). Why was such elaboration necessary? Did it really result in more or better knowledge than could have been obtained from much simpler studies?

Large Scale - why? Design Options ?

THE VITAL STATISTICS APPROACH

Many modern therapies and vaccines, including some of the most effective ones, such as smallpox vaccine, were introduced because preliminary studies suggested their value. Large-scale use subsequently provided clear evidence of efficacy. A natural -- and simple approach to the evaluation of the Salk vaccine would have been to distribute it as widely as possible, through the schools, to see whether the rate of reported polio was appreciably less than usual during the subsequent season. Alternatively, distribution might be limited to one or a few areas because limitations of supply would preclude effective coverage of the entire country. There is even a fairly good chance that were one to try out an effective vaccine against the common cold or against measles, convincing evidence might be obtained in this way.

THE OBSERVED CONTROL APPROACH

The difficulties of the vital statistics approach were recognized by all concerned, and the initial study plan, although not judged entirely satisfactory, got around many of the problems by introducing a control group similar in characteristics to the vaccinated group. More specifically, the idea was to offer vaccination to all children in the second grade of participating schools and to follow the polio experience not only in these children, but in the first and third-grade children as well. Thus the vaccinated second-graders would constitute the treated group, and the first- and third-graders would constitute the control group. This plan follows what we call the observed control approach.

RANDOMIZATION AND THE PLACEBO CONTROL APPROACH

The position of critics of the NFIP plan was that the issue of vaccine effectiveness was far too important to be studied in a manner which would leave uncertainties in the minds of reasonable observers. No doubt, if the vaccine should appear to have fairly high effectiveness, most public health officials and the general public would accept it, despite the reservations. If, however, the observed control scheme were used, a number of qualified public health scientists would have remained unconvinced, and the value of the vaccine would be uncertain. Therefore, the critics proposed that the study be run as a scientific experiment with the use of appropriate randomizing procedures to assign subjects to treatment or to control and with a maximum effort to eliminate observer bias. This plan follows what we call the placebo control approach.

** SEE ALSO... (on web site / video )
- Treatment of breast cancer
- US/British MD studies: prophylactic aspirin
- Effect of stretching before/after exercising on muscle soreness and risk of injury

| TABLE 1. Summary of Study Cases and Vaccination Status (Rates per 100,000) |
|-------------------|-----------------|---|
| STUDY GROUP       | STUDY POPULATION| Rate |
| All areas: Total  | 1,829,916       | 37  |
| Placebo control areas: Total | 749,236 | 36  |
| Vaccinated        | 200,745         | 16  |
| Placebo           | 201,229         | 57  |
| Not inoculated*   | 338,778         | 36  |
| Incomplete vaccinations | 8,484 | 12  |
| Observed control areas: Total | 1,080,680 | 38  |
| Vaccinated        | 221,998         | 17  |
| Controls**        | 725,173         | 46  |
| Grade 2 not inoculated | 123,605 | 35  |
| Incomplete vaccinations | 9,904 | 40  |

Source: Adapted from Francis (1955), Tables 2 & 3.

* Includes 8,577 children who received one or two injections of placebo.

** First- and third-grade total population.