STAT22000 Autumn 2013 Lecture 8

Yibi Huang

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3.1 Comparative Experiments
3.0 Observational Studies

Tale 1: Polio

- a contagious disease, attacks mostly children, may cause paralysis and death
- Present in past, but bad sanitation allowed people to contact mild versions of polio and develop antibodies
- Late 19th century: Better sanitation caused large epidemics
  - 1887: Stockholm, 44 deaths
  - 1905, 1911: Sweden
  - 1916: Polio epidemic first hit U.S.
    - NYC, one week, 301 deaths
    - Total: 27,000 cases, 6,000 deaths
  - 1921: FDR infected
  - 1952: 57,628 cases, 1-2K deaths, in U.S., intense pressure
- 1952: Salk developed a vaccine (Sabin's vaccine not ready)

How to test the effectiveness of the vaccine?

- give vaccine to children, and see if number of cases dropped?
- Why need a control group?

General Question: How to test whether or not a new drug, e.g., a new vaccine, is effective?

Basic method: **Comparison**

- Divide people (subjects) into two groups;
- Give the vaccine to one group (**treatment group**) and not to the other one (**control group**);
- Compare: if treatment group has lower rate of incidence, then the vaccine is effective

Key to the method: how to sensibly divide subjects.

Younger kids are more vulnerable.
If kids were divided by school grade (2nd year as treatment, 1st year as control), we are not sure if lower polio rates in the treatment is because the vaccine was effective or because the kids in the treatment group are more resistant.

Some other bad ideas to divide subjects

- by health, wealth, or gender
- by volunteer/non-volunteer

Definition: Confounding Variables

variables that can also explain the difference in the outcomes of the treatment group and control group

The two groups should be similar, and the only difference should be: **treated or not**

Possible Strategies to Combat Confounding

For example, *age* is a confounder with the effect of the vaccine

- *restricting* the confounder (e.g. study only 6-yr-old kids)
- *balancing* (e.g. make the age compositions in the treatment and control group similar)

A simple way to ensure balance: **Randomization**,
which means assigning subjects to the treatment and control groups **randomly**
This design is called the **completely randomized design**

- Randomly $\neq$ Haphazardly
- To avoid human factors, use coin tossinging/random number table/random number generator.
- By law of large number, the treatment and control groups should be similar in all aspect.

Example: Polio Vaccine (Cont'd)

Need parents' permission to vaccinate their kids.

The randomized controlled double-blind experiment

	Size	*Rate* (# of cases per 100,000)
Treatment	200,000	28
Control	200,000	71
No consent	350,000	46

1. Which pair of rates shows the vaccine is effective?
2. Neither the control group nor the no-consent group got the vaccine, but the no-consent group had a lower rate of polio. Why?

3. Can we assign all volunteers to the treatment group, and all non-volunteers to the control group?

Why Volunteers Were More Vulnerable to Polio?

- Higher income parents more likely to consent to treatment;
- Higher income → more hygiene environment → less chance to contract mild cases of polio in early childhood → less chance to develop antibodies to polio;
- So, volunteers are more vulnerable to polio;

If treatment = volunteers, control = non-volunteers,

- the effect of being volunteer/non-volunteer will be **confounded** with the effect of the treatment.

Blinding

1. **Single blind**: Do not let subjects know which group they are in: give "fake" vaccine (**placebo**) to control group;
   - Example: Placebo can relive pain for some people
   - Knowing being treated or not might be confounding;
2. **Double blind** — Neither the subject nor those who evaluate the outcome (e.g., diagnosing the disease) know which ones get treated by the new vaccine;
   - Avoid the subjectivity of evaluators

Randomized Block Design — a More Elaborate Experimental Design

- Similar subjects are combined as "blocks."
- The factors taken into account to form the blocks are thought to be likely, *a priori*, to have an influence on the observed response
- Within each block, subjects are assigned at random to treatments.
- Example 1: In agricultural studies, fields are divided into blocks since adjacent fields are likely to be similar in fertility, humidity...
- Example 2: blocking on batches of material used

Matched Pair Design

- a special case of the randomized block design
- comparing **two** groups only (treatment + control)
- Subjects are match in pairs so that subjects in a pair are as "similar" as possible (concerning all variables we deem influential: like, gender, age, medical history, etc.)
- Within each pair, we determine randomly (coin toss) who gets which treatment.

Example: Many medical experiments are done on

- identical twins, or
- the same individual under two different conditions

Example of a Matched Paired Design

- Goal: Comparing two treatments for the rehabilitation of acidified lakes
- Only 6 lakes are allowed to experiment on
- If using completely randomized design: randomly assign 3 of the 6 lakes to the first treatment, and the rest 3 lakes the second
- However, here is tremendous lake to lake variability
- Technology allows us to split each lake in two using a plastic "curtain" and treat the halves separately.
- So each lake is a block, and the two halves are randomly assigned to one of the two treatments

Example

In an experiment to study the effects of hunger on recall memory, participants are asked to come in twice to complete a memory task.

- In the first session, participants are told to fast for 24 hours before coming in.
- In the second session, participants are given a meal before the task.
- The two visits of an individual form a matched pair.
- Problem?
  - learning effect
- Solution?
  - **randomize** the order of the two sessions (hungry vs. meal)

Observational Studies v.s. Experiments

Our textbook [IPS7e] differentiate observational studies and experiments as follows:

- in an **observational study**, the researcher observes individuals and measures variables of interest but do not attempt to influence the responses.
- In an **experiment**, the researcher deliberately imposes some treatment on individuals to observe their responses.

Most other books differentiate the two as follows

- in an **observational study**, the allocation of subjects to the two groups is **NOT** under the control of the investigators;
- in an **experiment**, the investigators control the allocation of subjects to the treatment group and the controlled group

Observational Studies

- Many studies in social science and public health are observational studies.
- Example: to study the effect of smoking on health
  - Treatment group ("exposed group"): smokers;
  - Control group: no-smokers;
- Since the investigators have no control over allocation, the treatment group and control group might be different in important aspects other than the treatment, i.e., **there are many confounding variables**.
- Observational studies suggest **association**, not **causation**!

Which of the following studies is observational? Which is experimental? Why?

- Consider two treatments for breast cancer
  - Treatment A: removal of the breast,
  - Treatment B: removal of the tumor followed by radiation

  A medical team examines the records of 25 large hospitals, classifies them into two groups based on the treatments taken, and compares the survival times after surgery of the patients in the two groups.
- Assigning some mice to high doses of saccharine and some to a control diet, and observing their respective incidences of cancer.

Kidney Stone Surgeries

A study in 1994 compared 2 surgeries for removing kidney stones:

- open surgery
- percutaneous nephrolithotomy (PN): a "keyhole" surgery that removes the stone through the skin

The most recent 350 surgeries for each of the two types were investigated, and found that 83% of the PN surgeries were successful, compared to 78% in the open surgery.

Does this show the PN surgery is better?

Size of Stones	Open Surgery			PN Surgery		
	success	failure	success rate	success	failure	success rate
$<$ 2cm	81	6	$\frac{81}{87} = 93\%$	234	36	$\frac{234}{270} = 87\%$
$\geq$ 2cm	192	71	$\frac{192}{263} = 73\%$	55	25	$\frac{55}{80} = 69\%$
Total	273	77	$\frac{273}{350} = 78\%$	289	61	$\frac{289}{350} = 83\%$

The size of stones is a confounding variable.

Controlled Experiment on Clofibrate

	Clofibrate		Placebo	
	Number	Deaths	Number	Deaths
Adherers	708	15%	1813	15%
Non-adherers	357	25%	882	28%
Total group	1103	20%	2798	21%

- Is Clofibrate effective?
- Adherers v.s. non-adherers in the treatment group
  Does this mean that Clofibrate is actually effective?
- Adherers v.s. non-adherers in the control group
- Conclusion
  - Clofibrate has no effect;
  - Adherers are different from non-adherers;

Historical and Contemporaneous Controls

- Sometimes randomized controlled experiments are hard to do (e.g., for ethical reasons);
- Compare patients by the new treatment with **historical controls**: patients treated in the old way **in the past**;
- In contract, in randomized controlled experiments, subjects in both groups are chosen from a population at the same time period (**contemporaneous controls**);
- Historical controls may not be reliable because the treatment group and the historical control group may differ in important ways.
- Studies using historical controls are *observational studies*