Salk Vaccine Field Trial

By the 1950s, polio killed several hundreds of thousands of victims, especially children. Several vaccines were being developed; Jonas Salk's vaccine was thought to be the best.

In 1954, Public Health Service and National Foundation for Infantile Paralysis (NFIP) wanted to use the vaccine on humans.

What if the NFIP had just given the vaccine to large numbers of children in 1954? If the number of cases drops, the vaccine is effective???

Wrong. The number of polio cases changes year-to-year. So a drop doesn't necessarily mean the vaccine is effective.

Instead:

purposely not give the vaccine to a *control group*;
give the vaccine to a *treatment group*;
compare both incidence rates and see how the vaccine does.

Children can only be vaccinated with parents' permission. So NFIP thought to use those who gave permission as the treatment group and those who didn't as controls. Problem?

This design *biases* against the vaccine. Children of higher-income parents more likely to have permission and more likely to contract polio. The difference in response may be *confounded* by having higher-income families in the treatment group and lower-income families in the control group.

Another proposed design: vaccinate all grade 2 children with consent; leave grade 1 and grade 3 children as controls. Problem?

Polio is contagious and spreads through contact. Incidence might be higher in grade 2 than in 1 or 3. (biases study against vaccine). Or incidence might have been lower in grade 2 (biases study for vaccine).

Our treatment group and control group should be as similar as possible.

Salk Vaccine Study Design

Control group and treatment group both from the same population: children whose parents gave permission.
(removing confounding effect of family background).

Rather than using human judgment, children were assigned randomly (like flipping a coin). (referred to as *randomized controlled*).

Children in the control group were given an injection of salt dissolved in water as a *placebo*. The children did not know what group they were in; any difference in polio incidence was attributable to the vaccine and not the idea of the vaccine.

After "treating" all the children, the doctors had to diagnose who contracted polio. Many forms of polio are hard to diagnose; if the doctors knew who had not been given the vaccine, they would probably be more likely to diagnose polio. So the experiment was *double-blinded*. Neither the subjects nor the doctors knew who was in the treatment or control groups.

Results:

Treatment	200,000 children	28 cases of polio per 100,000
Control	200,000 children	71 cases of polio per 100,000
No consent	350,000 children	46 cases of polio per 100,000

They removed as much bias as they could from the study design. If the vaccine had no effect, the child should have the same chance of contracting polio in the treatment group or the control group. How likely is it to see something as extreme as 28 and 71? Not very likely.

The vaccine is effective.

Controlled Experiments

- Statisticians use the method of comparison
- Want to know effect of *treatment* on *response*
- compare responses of *treatment group* to a *control group*
  - if control group "looks like" treatment group, differences in response likely due to treatment
  - if control group "does not look like" treatment group, differences in response may be confounded by differences in the group
- Subjects are assigned to treatment and control groups randomly - *randomly controlled experiments*
- If possible, control group is given a *placebo* which resembles the treatment; subjects should not know in which group they are
- Even better - *double-blind experiment*:

  subjects do not know in which group they are;

  evaluators do not know to which groups the subjects belong

Randomized controlled experiments are hard to do. Often studies compare a treatment group to a *historical control* group or a group from the past.

One major problem with this approach is that it assumes that nothing has changed with time, i.e. controls in 1990 are the same as controls in 2006. Not true.

A good randomized controlled experiment uses *contemporaneous controls* or controls from the same time period. That way we can eliminate possible confounding due to change in time period.

Looking at Effects of Smoking

You're not likely to find a group of people who will take up smoking for ten years just in the name of statistics. You can't force subjects into treatment or control groups based on some random assignment.

People are smokers or nonsmokers. They assign themselves.

So what can we do?

Identify groups of smokers and nonsmokers and then *observe* what happens to each group.

We might see that heart attacks, lung cancer, and other diseases are more common among smokers. We would say that there is an *association* between smoking and disease.

However, we cannot say that smoking *causes* disease. There may be some other factor that drives whether or not you smoke and whether or not you have heart disease. This factor may *confound* your results.

How could we fix this? We could compare two groups of patients with similar heart disease, one group of smokers and one group of non-smokers. Because both groups have heart disease, we have controlled the effect of heart disease in our comparison.

Confounding factors can make observational studies very misleading.

Clofibrate Trial

Coronary Drug Project - randomized, controlled double-blind exp.

Objective: evaluate five drugs for prevention of heart attacks.

8,341 subjects: 5,552 assigned treatment; 2,789 assigned control.

Patients were followed for five years.

One of the tested drugs was clofibrate:

20% of the group died over 5 years; 21 % died in the control group.

People suggested that the reason clofibrate didn't work was that subjects did not take their medicine.

So they took a closer look at the clofibrate group, specifically at those who *adhered* or followed the instructed protocol.

Among adherers, 15% died; among non-adherers, 25% died.

Conclusion: If you take it, clofibrate works.

However, when they examined the control group by adherence, they saw a similar pattern:

Among adherers, 15% died; among non-adherers, 28% died.

(Note that adherence is an observational study. Although we were doing a controlled experiment, the investigators had no control over who adhered and who didn't.)

Conclusion:

Clofibrate does not have an effect.

Adherers are different from non-adherers

Why would adherers (of treatment or control status) live longer?

Observational Studies

- Investigators do not assign subjects to treatment or control. Subjects are assigned to the treatment group if they happen to have the condition being studied. The others are the controls.
- Observational studies establish a link between two things or *association*. Note that association does not prove causation.
- A *confounder* is a third variable that is related to both the exposure of interest and the response.
- The effects of the treatment may be confounded by factors related to which group the subjects were assigned.
- These confounding factors can sometimes be *controlled for* by comparing smaller groups that are homogenous wrt the confounder.