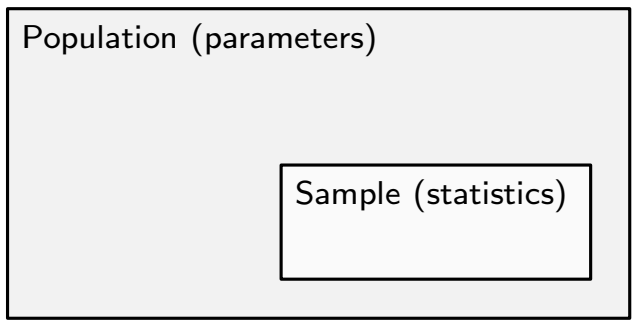
Math 207: Statistics

Controlled Experiments



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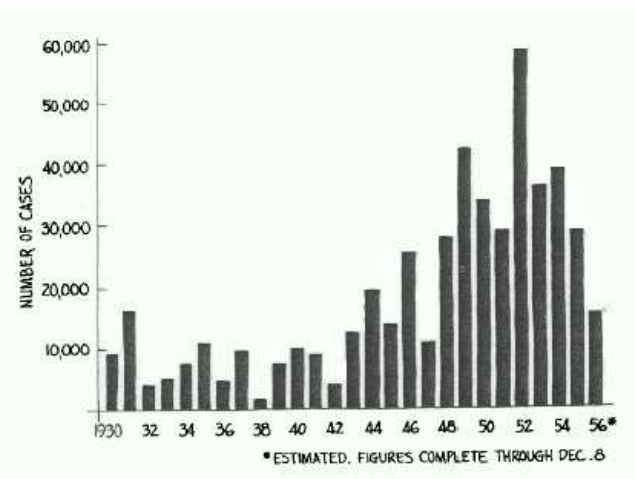
Polio

- Viral infectious disease: victims are typically children
- Can effect nervous system causing muscle weakness or paralysis
- Most cases cause no symptoms but can spread the disease
- Major epidemics across the world between 1910 and 1956
- Vaccines discovered in 1950s have made polio rare in most countries

Polio Victim



Infection Statistics

Jonas Salk

Vaccine Trial Design Proposals

- 1954: Salk vaccine ready to tested outside the laboratory
- Public Health Service and National Foundation for Infantile Paralysis (NFIP) designed the experiments
- Trials involved 2,000,000 grade 1–3 children in school districts across the US
  - 500,000 vaccinated
  - 1,000,000 deliberately left unvaccinated, as controls
  - 500,000 refused vaccination
- Vaccine Trial Design Proposals
  - Vaccinate a large number of children in 1954 and compare the polio incidence rate to that in 1953 (not used: see the graph on slide 1)
  - Vaccinate all grade 2 children whose parents consent; leave children in grades 1 and 3 as controls (used in some school districts)
  - From the set X of children whose parents consent, randomly select some for vaccination; leave others in X as controls (used in some school districts)

Complicating Factors

Challenges

- Children could not be vaccinated without parental consent
- Higher-income parents were more likely to give consent
- Children of higher-income families were more vulnerable to polio
- Some cases are difficult to diagnose
- Infection rate can vary from grade to grade

Solutions

- Treatment and control groups should be as similar as possible, except for the treatment.
- Use randomness rather than human judgment to assign subjects to groups and avoid bias.

Trial Results

Randomized controlled double-blind experiment			NFIP study		
	Size	Rate*		Size	Rate*
Treatment	200,000	**28**	Grade 2 (vaccine)	225,000	25
Control	200,000	**71**	Grades 1 and 3 (control)	725,000	**54**
No consent	350,000	46	Grade 2 (no consent)	125,000	**44**

*Rate is number of cases per 100,000 subjects. Green = consent Gray = consent + no consent

- Blue values demonstrate vaccine effectiveness: Could the **71** $\rightarrow$ **28** difference be due to the 50/50 selection chance?
- Red values demonstrate that the NFIP study treatment and control groups differed in their vulnerability
- **71** $\rightarrow$ **28** vs **54** $\rightarrow$ 25 shows bias in NFIP study due to confounding
- Average of blue values (50) differs from 46: children of consenting parents were more vulnerable

Vaccine Trial Concepts

- Treatment group: children selected for vaccination
- Control group: children selected not to be vaccinated
- Comparison: estimate the effectiveness of the vaccine by comparing the infection rates (responses) of the two groups
- Double-blind: neither the subjects nor the medical examiners knew who was in the treatment group and who was in the control group
- Placebo: children in the control group were given an injection of salt water
- Confounding: a difference (such as family income) between the treatment and control groups — other than the treatment — which affects the responses being studied.
- Random: chosen without regard to any characteristics of the individual members of the population so that each has an equal chance of being selected.

Cirrhosis of the Liver

- Cirrhosis of the liver: multiple causes including alcoholism and hepatitis B/C
- Without a liver transplant, outcomes are usually poor
- A possible complication is internal bleeding that results in death
- Surgery to redirect blood flow through a portacaval shunt has been studied as a potential treatment
- The procedure is long and hazardous
- Numerous studies have been conducted to asses the value of the surgery
  - 32 without controls
  - 15 with non-randomized controls
  - 4 with randomized controls

Results of Studies

- Of the 51 studies conducted to assess the effect of the surgery:
  - 75% of studies without controls were markedly enthusiastic about shunt
  - 67% of non-randomized studies were markedly enthusiastic
  - 0% of randomized studies were markedly enthusiastic

	Degree of enthusiasm		
Design	Marked	Moderate	None
No controls	24	7	1
Controls, but not randomized	10	3	2
Randomized controlled	0	1	3

- Three-year survival rates show that subjects selected for surgery in the non-randomized studies were healthier than the controls

	Randomized	Not randomized
Surgery	60%	60%
Controls	60%	45%

Coronary Artery Disease Therapies

- Randomized controlled experiments can be hard to do.
- Treatment groups are often compared to historical rather than contemporaneous controls.

Therapy	Randomized controlled		Historically controlled	
	+	−	+	−
Coronary bypass surgery	1	7	16	5
5-FU	0	5	2	0
BCG	2	2	4	0
DES	0	3	5	0

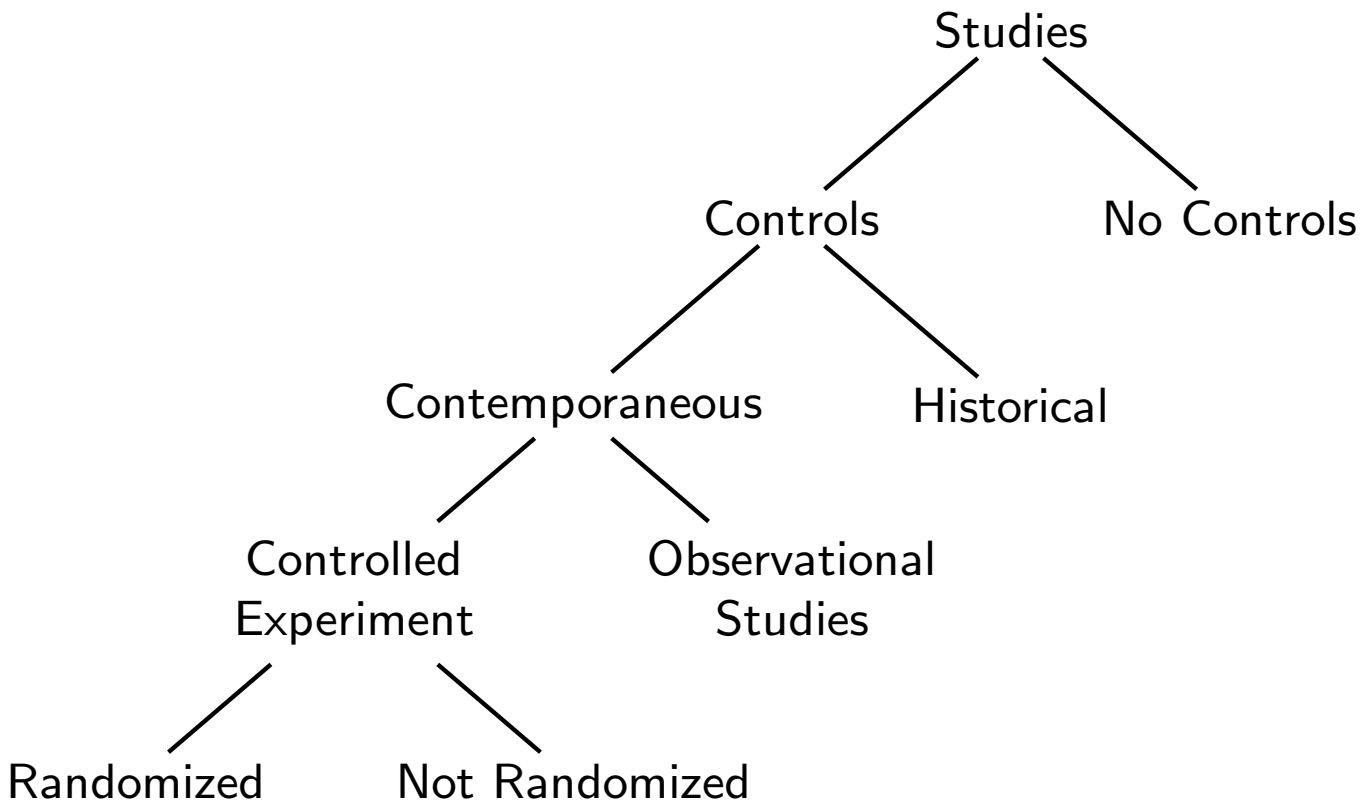
- Three-year survival rates for surgery patients and controls show that that the treatment and historical control groups differed: patients selected for surgery were healthier.

	Randomized	Historical
Surgery	87.6%	90.9%
Controls	83.2%	71.1%

Controlled Experiments vs Observational Studies

- **Controlled experiment**: Investigators decide who will be in the treatment group and who will be in the control group
  - Example: Salk vaccine trials discussed in Chapter 1
  - Example: Coronary Drug Project discussed in Section 2.2
  - The control and treatment populations are similar — except in the application of treatment
- **Observational study**: Subjects assign themselves to the groups
  - Example: Smoking studies
  - **Association** between treatment and outcome is circumstantial evidence for causation.
  - Association does not prove causation. **Confounding** factors may exist.
  - Observational studies can be powerful tools but can also be misleading.
    - Were the control and treatment groups similar?
    - Did the two populations differ in ways other than the treatment?
  - Technique: compare small, more homogeneous groups (e.g., age, sex)

Classification of Studies



Clofibrate

- Coronary Drug Project: randomized, controlled double-blind experiment (placebo = lactose) to evaluate heart attack prevention drugs
- 8,341 patients followed for five years (5,552 got treatment, 2,789 controls)
- Clofibrate: a cholesterol reduction drug evaluated in the study
- Comparing 20% to 21% shows that clofibrate did not save lives.
- Many subjects did not take their medicine (non-adherers).
- Compare 15% to 15% (not to 21% or 25%) to control for adherence.

	Clofibrate		Placebo	
	Number	Deaths	Number	Deaths
Adherers	708	15%	1,813	15%
Non-adherers	357	25%	882	28%
Total group	1,103	20%	2,789	21%

- Conclusions: (i) Clofibrate does not have an effect. (ii) Adherers are different from non-adherers.

Confounding Factors and Associations

- Pellagra: Among many associations between the 18^{th} century disease and other factors, lack of niacin was found to be the underlying cause.
- Cervical Cancer and Circumcision: Human papilloma virus was found to be the underlying cause and explained differences in cancer rates between particular populations in the 1950s.
- Ultrasound and low birthweight: The confounding factor of problem pregnancy was found to explain an association between ultrasound and low birthweight. Randomized controlled experiments showed that ultrasounds may be protective.
- The Samaritans and Suicide: A confounding factor explained an association between the expansion of a volunteer welfare organization and a decrease in the English suicide rate in 1964–1970.

Confounding

- **Confounding**: A difference between the treatment and control groups — other than the treatment — that affects the responses being studied
- Confounders must be assocated with both:
  - The disease/outcome and
  - The exposure/treatment.
- Hidden confounders are a major problem in observational studies.
- Examples:
  - NFIP polio vaccine study: family income
  - Portacaval shunt studies: health of patients selected for surgery
  - Coronary bypass surgery studies: health of patients selected for surgery
  - Cervical cancer study: sexual activity

- Observational study on sex bias in admissions at UC, Berkeley in 1973
  - 44% of 8,442 male applicants were admitted
  - 35% of 4,321 female applicants were admitted
- Compare admissions to the six largest majors:

	Men		Women	
Major	Number of Applicants	Percent Admitted	Number of Applicants	Percent Admitted
A	**825**	**62**	**108**	**82**
B	560	63	25	68
C	325	37	593	34
D	417	33	375	35
E	**191**	**28**	**393**	**24**
F	373	6	341	7

- Major A: Less selective but few women and many men applied
- Major E: Highly-selective but many women and few men applied
- Simpson's paradox: Relationships between percentages in subgroups can be reversed when the subgroups are combined.