

Math 207: Statistics

Chapters 1–2: Controlled Experiments

Population (parameters)

Sample (statistics)

Dr. Ralph Wojtowicz

Mathematics Department



SHENANDOAH
UNIVERSITY

Polio

Polio

- Viral infectious disease: victims are typically children
- Can effect nervous system causing muscle weakness or paralysis



Polio Victim

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



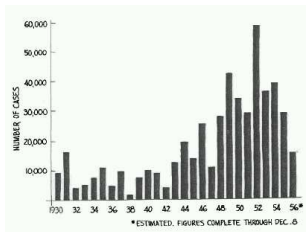
Polio Victim

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



Polio Victim



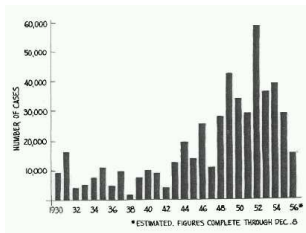
Infection Statistics

Polio

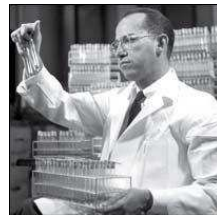
- Viral infectious disease: victims are typically children
- Can effect nervous system causing muscle weakness or paralysis
- Most cases cause no symptoms but can spread the disease
- Major epidemics across the world between 1910 and 1956
- Vaccines discovered in 1950s have made polio rare in most countries



Polio Victim



Infection Statistics



Jonas Salk

Vaccine Trial Design Proposals

Vaccine Trial Design Proposals

- 1954: Salk vaccine ready to be tested outside the laboratory

Vaccine Trial Design Proposals

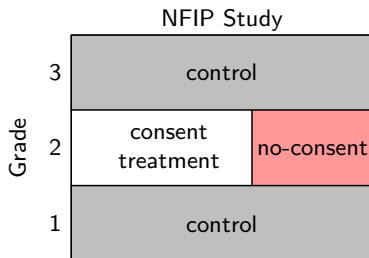
- 1954: Salk vaccine ready to be tested outside the laboratory
- Vaccine Trial Design Proposals:

Vaccine Trial Design Proposals

- 1954: Salk vaccine ready to be tested outside the laboratory
- 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 ??)

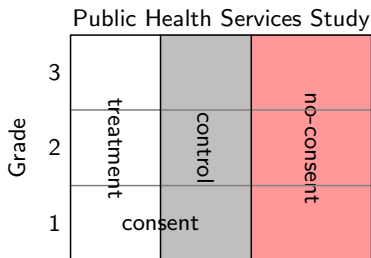
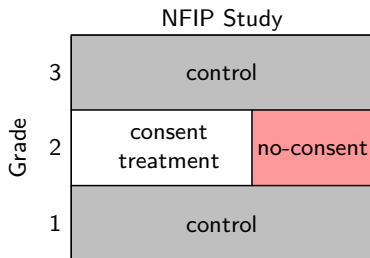
Vaccine Trial Design Proposals

- 1954: Salk vaccine ready to be tested outside the laboratory
- 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 ??)
 - Vaccinate all grade 2 children whose parents consent; leave children in grades 1 and 3 as controls (used in some school districts)



Vaccine Trial Design Proposals

- 1954: Salk vaccine ready to be tested outside the laboratory
- 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 ??)
 - 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

Trial Results

NFIP Study

	Size	Rate*
Grade 2 (vaccine)	225,000	25
Grades 1 and 3 (control)	725,000	54
Grade 2 (no consent)	125,000	44

*Rate is number of cases per 100,000 subjects.

NFIP Study

3	control	
2	consent treatment	no-consent
1	control	

Trial Results

NFIP Study

	Size	Rate*
Grade 2 (vaccine)	225,000	25
Grades 1 and 3 (control)	725,000	54
Grade 2 (no consent)	125,000	44

Public Health Services Study

	Size	Rate*
Treatment	200,000	28
Control	200,000	71
No consent	350,000	46

*Rate is number of cases per 100,000 subjects.

NFIP Study

Grade 3	control	
Grade 2	consent treatment	no-consent
Grade 1	control	

Public Health Services Study

Grade 3	treatment	control	no-consent
Grade 2			
Grade 1	consent		

Trial Results

NFIP Study

	Size	Rate*
Grade 2 (vaccine)	225,000	25
Grades 1 and 3 (control)	725,000	54
Grade 2 (no consent)	125,000	44

Public Health Services Study

	Size	Rate*
Treatment	200,000	28
Control	200,000	71
No consent	350,000	46

*Rate is number of cases per 100,000 subjects.

NFIP Study

Grade 3	control	
Grade 2	consent treatment	no-consent
Grade 1	control	

Public Health Services Study

Grade 3	treatment	control	no-consent
Grade 2			
Grade 1	consent		

- Blue values demonstrate vaccine effectiveness: Could the 71 → 28 be due to chance?

Trial Results

NFIP Study

	Size	Rate*
Grade 2 (vaccine)	225,000	25
Grades 1 and 3 (control)	725,000	54
Grade 2 (no consent)	125,000	44

Public Health Services Study

	Size	Rate*
Treatment	200,000	28
Control	200,000	71
No consent	350,000	46

*Rate is number of cases per 100,000 subjects.

NFIP Study

3	control	
2	consent treatment	no-consent
1	control	

Public Health Services Study

3	treatment	control	no-consent
2			
1	consent		

- Blue values demonstrate vaccine effectiveness: Could the 71 → 28 be due to chance?
- Red values demonstrate that difference between NFIP treatment and control groups.

Trial Results

NFIP Study

	Size	Rate*
Grade 2 (vaccine)	225,000	25
Grades 1 and 3 (control)	725,000	54
Grade 2 (no consent)	125,000	44

Public Health Services Study

	Size	Rate*
Treatment	200,000	28
Control	200,000	71
No consent	350,000	46

*Rate is number of cases per 100,000 subjects.

NFIP Study

Grade 3	control	
Grade 2	consent treatment	no-consent
Grade 1	control	

Public Health Services Study

Grade 3	treatment	control	no-consent
Grade 2			
Grade 1	consent		

- Blue values demonstrate vaccine effectiveness: Could the 71 → 28 be due to chance?
- Red values demonstrate that difference between NFIP treatment and control groups.
- 71 → 28 vs 54 → 25 shows bias in NFIP study due to confounding.

Trial Results

NFIP Study

	Size	Rate*
Grade 2 (vaccine)	225,000	25
Grades 1 and 3 (control)	725,000	54
Grade 2 (no consent)	125,000	44

Public Health Services Study

	Size	Rate*
Treatment	200,000	28
Control	200,000	71
No consent	350,000	46

*Rate is number of cases per 100,000 subjects.

NFIP Study

3	control	
2	consent treatment	no-consent
1	control	

Public Health Services Study

3	treatment	control	no-consent
2			
1	consent		

- Blue values demonstrate vaccine effectiveness: Could the 71 → 28 be due to chance?
- Red values demonstrate that difference between NFIP treatment and control groups.
- 71 → 28 vs 54 → 25 shows bias in NFIP study due to confounding.
- Average of blue values (50) differs from 46: PHS consent group was 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 assess 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

Design	Degree of enthusiasm		
	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

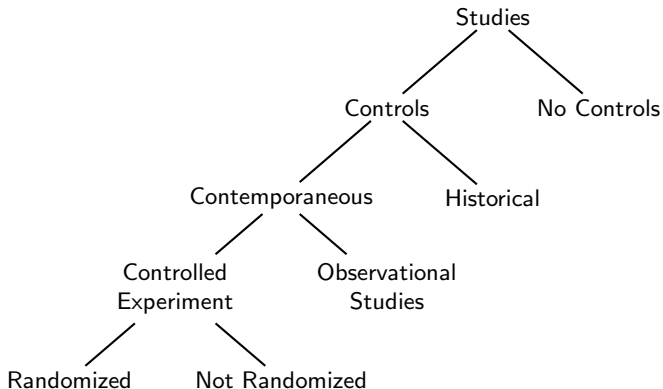
- Three-year survival rates for surgery patients and controls show that that the treatment and historical control groups differed: patients selected for surgery were healthier.

	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 19–20th 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 associated 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:

Major	Men		Women	
	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.