

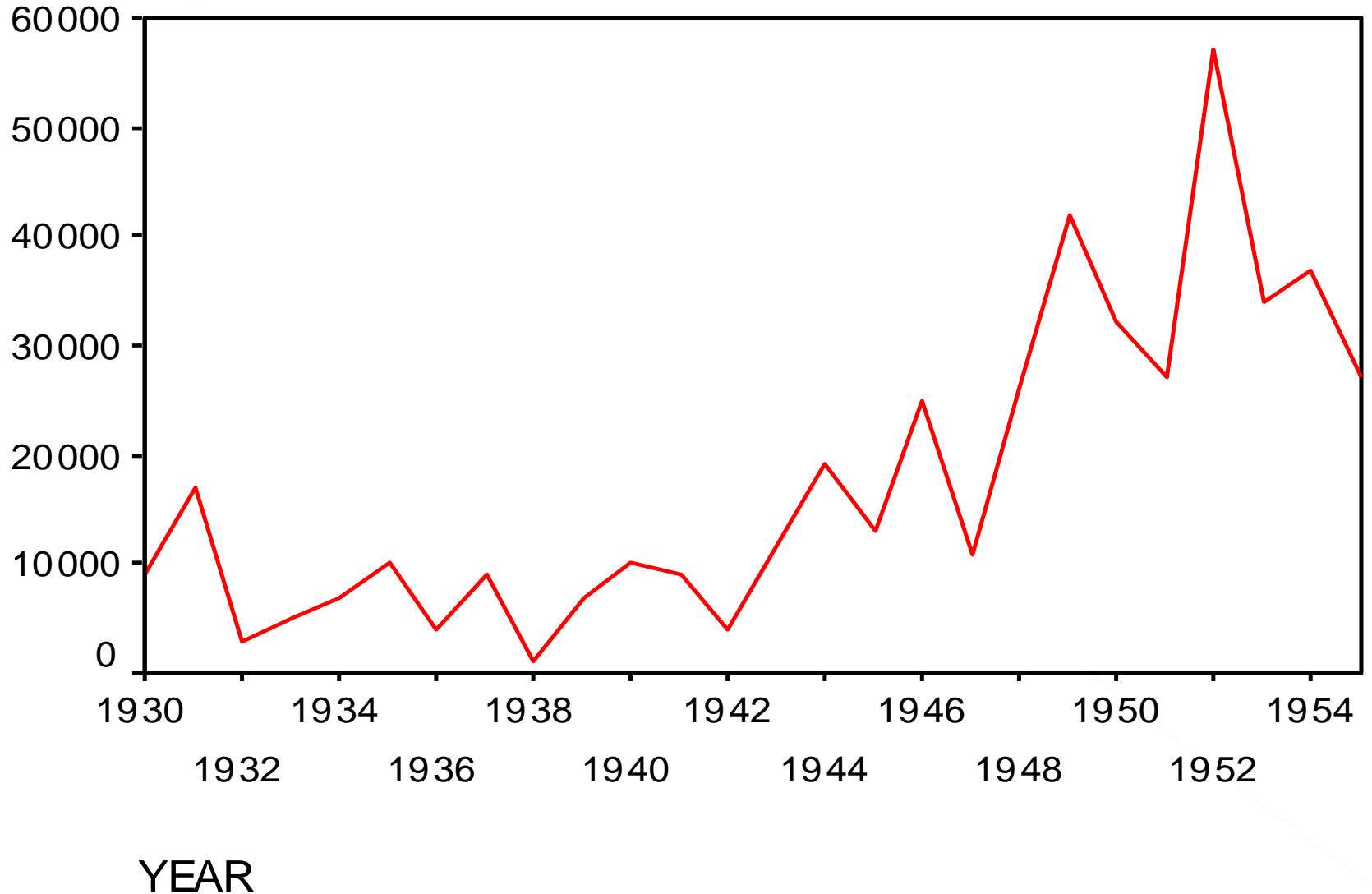
1954 Salk polio vaccine trials

- ▶ Biggest public health experiment ever
- ▶ Polio epidemics hit U.S. in 20th century
- ▶ Struck hardest at children
- ▶ Responsible for 6% of deaths among 5- to 9-year-olds



Number of polio cases in the U.S.

1930 to 1955



Salk vaccine trial: Background

- ▶ Polio is rare but the virus itself is common
- ▶ Most adults experienced polio infection without being aware of it.
- ▶ Children from higher-income families were more vulnerable to polio!
- ▶ Children in less hygienic surroundings contract mild polio early in childhood while still protected from their mother's antibodies. They develop immunity early.
- ▶ Children from more hygienic surroundings don't develop such antibodies.

Salk trial: The need for testing

- ▶ By 1954, Salk's research with a vaccine looked promising
- ▶ Government agencies were ready to try the vaccine in the general population but some scientists feared the vaccine was unsafe or ineffective.
- ▶ There was enormous fear and desperation throughout the country.
- ▶ Why not just distribute the vaccine to some and see if it lowered the polio rate?
 - A yearly drop might mean the drug was effective, or that that year was not an epidemic year
- ▶ Vaccine could not be distributed without **testing**

Salk vaccine trial: The need for controls

- ▶ An experiment requires **controls**.
- ▶ To test if the vaccine was effective the only variable that should be considered is the vaccine itself
- ▶ This means that some children would get the vaccine and some would not.
- ▶ This raises enormous ethical questions:
 - Is it ethical to not give children the vaccine?
 - Imagine yourself as a parent in these desperate times. Would you participate in such an experiment.
 - Ultimately, does the benefit to society outweigh the risk to those children who would not get the vaccine?

Salk vaccine: The need for massive trials

- ▶ Polio rate of occurrence is about 50 per 100,000
- ▶ Suppose the vaccine was 50% effective and 10,000 subjects were recruited for each of the control and treatment groups
 - You would expect 5 polio cases in control group and 2-3 in treatment group
 - Such a difference could be attributed to random variation
- ▶ Clinical trials were needed on a massive scale
- ▶ The ultimate experiment involved over 1.6 million children, with over 600,000 children inoculated

Controversy over the design of the experiment

- ▶ In order to isolate the vaccine as the only variable to be considered, the **treatment** and **control** groups need to be as similar as possible
- ▶ But how should subjects be recruited?
- ▶ **Fact:** volunteers tend to be better educated and more well-to-do than those who don't participate
- ▶ In the context of the polio disease, relying on volunteers could potentially **bias** the results
 - Subjects would tend to have higher rates of polio
 - Subjects are not representative of the population
 - Results would be biased **against the vaccine**
- ▶ After much debate, the trials proceeded with two different protocols.

“Observed Control” approach

- ▶ Administer the experiment to 1st, 2nd, and 3rd graders
- ▶ Offer the vaccination to 2nd graders
 - This group would rely on volunteers (parental consent)
- ▶ Use 1st and 3rd graders as control group
 - These children would be observed for incidences of polio
- ▶ Supporters of this approach argued that there would not be much variability between grades so treatment and control groups would be similar
- ▶ And the control group would be “observed controls”
- ▶ But there were objections . . .

NFIP Observed Control study

- ▶ Volunteers would result in more children from higher income families in treatment group
 - Treatment group is thus more vulnerable to disease than control group
 - Would expect more incidences of polio in the treatment group than in the control group
 - Biases the experiment against the vaccine
- ▶ How would incidents of the disease be diagnosed?
 - Many forms of polio are hard to diagnose
 - In making the diagnosis physicians would naturally ask whether a child was vaccinated or not
 - Diagnosis for borderline cases could be affected by knowledge of what grade the child was in and whether the child was vaccinated or not

Randomized control approach

- ▶ This experiment relied on volunteer subjects overall.
- ▶ But subjects were **randomly assigned** to treatment and control groups
- ▶ Control group was given a **placebo**
- ▶ Placebo material was prepared to look exactly like the vaccine so subjects didn't know what treatment they were getting
- ▶ Placebo-control group guards against the "placebo effect"
- ▶ Many objected to the design on ethical grounds.
- ▶ Jonas Salk himself called it "A 'beautiful' experiment over which the epidemiologist could become quite ecstatic but which would make the humanitarian shudder."



Randomized control approach

- ▶ Subjects were “blind”: they did not know to which group they were assigned
- ▶ Also, those doing the evaluation didn't know which treatment any subject received
- ▶ Each vial was identified by a code number so no one involved in the vaccination or the diagnostic evaluation could know who got the vaccine.
- ▶ Experiment was **double-blind**: neither subjects nor those doing the evaluation knew which treatment any subject received



Results of vaccine trials

The randomized, controlled experiment

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

The Observed Control study

	Size	Rate (per 100,000)
Grade 2 (vaccine)	225,000	25
Grade 1, 3 (control)	725,000	54
Grade 2 (no consent)	125,000	44

Source: Thomas Francis, J r., "An evaluation of the 1954 Poliomyelitis vaccine trials---summary report," *American Journal of Public Health* vol 45 (1955) pp. 1-63.

Comparing the two studies

- ▶ Results show that the observed control study was biased against vaccine
 - Treatment group got the vaccine but was more prone to higher polio rates
 - Control group didn't get the vaccine but was more prone to lower polio rates
- ▶ It's impossible to determine what's the effect of the vaccine and what's the effect of socio-economic status
- ▶ This is called **confounding**—the inability to distinguish the separate impacts of two or more variables on a single outcome.
- ▶ In a randomized controlled experiment, by making the treatment and control groups as similar as possible (by randomization), we are able to isolate the variable of interest and eliminate confounding

Comparing the two studies: are the results “significant”?

- ▶ In the “observed control” approach, chance enters the study in an unplanned and haphazard way based on what families will volunteer
- ▶ By contrast, for the randomized controlled experiment chance enters the study in a planned and simple way
 - Each child has 50-50 chance to be in the treatment or control group
- ▶ This allows for the use of probability to analyze the results

Are the results significant?

- ▶ Two competing positions—which side would you be on?
 - **Pro:** “The vaccine is effective. There were less cases of polio in the treatment group than in the control group. We should undertake a massive vaccination program throughout the general population.”
 - **Con:** “We are not convinced. The two groups were randomly divided. There may have been fewer polio-prone people in the treatment group. It was all done by chance. We can’t be sure and we’re not willing to commit millions of dollars of taxpayer’s money on a vaccination program that might not be effective.”

Are the results **significant**?

- ▶ Assume the cons are right and that the vaccine is worthless. **What are the chances of seeing such a large difference in the two groups?**
- ▶ Imagine a “polio” coin where the chance of heads is equal to the chance that a person gets polio. Flip the coin in Room A for 200,000 times. Then flip it in Room B for 200,000 times. What’s the chance that we would get such a large difference as 28 heads in A and 71 heads in B?
- ▶ They are over a billion to one against!
- ▶ In the face of such odds, we say that the outcome is **statistically significant**. The effect is so large that it would rarely occur by chance.



Salk vaccine trials aftermath

- ▶ The results, announced in 1955, showed good statistical evidence that Jonas Salk's vaccine was 80-90% effective in preventing paralytic poliomyelitis.
- ▶ **Postscript:** Polio was virtually eliminated from the Americas in 1994, but still circulates in Asia and Africa, paralyzing the world's most vulnerable children.
- ▶ The Global Polio Eradication Initiative was begun in 1988. That year, an estimated 350,000 children were paralyzed with polio worldwide.
- ▶ In 2004, polio cases had fallen to just over 1,200 cases globally.