1955 Polio Vaccine Trial Announcement

"Safe, effective, and potent."

With these words on April 12, 1955, Dr. Thomas Francis Jr., director of the Poliomyelitis Vaccine Evaluation Center at the University of Michigan School of Public Health, announced to the world that the Salk polio vaccine was up to 90% effective in preventing paralytic polio.

Dr. Francis made the announcement to a crowd of scientists and reporters at the University of Michigan's Rackham Auditorium, concluding his two-year national field trials of the poliomyelitis vaccine developed by his former student, Jonas Salk. Francis was chair of the School of Public Health Department of Epidemiology where Salk did postgraduate training.

Over 1,800,000 children participated in the field trials, which were unprecedented in magnitude.

ANN ARBOR: The vaccine works. It is safe, effective, and potent.

Dr. Thomas Francis, Jr., UM Director of the Poliomyelitis Vaccine Evaluation Center, told an anxious world of parents that the Salk vaccine has been proved to be up to 80-90 percent effective in preventing paralytic polio.

At a meeting of over 500 scientists and physicians and before the penetrating eyes of cameras and powerful spotlights, Dr. Francis spoke on the effectiveness of the Salk vaccine. The meeting was held at the Rackham Auditorium in Ann Arbor under the joint sponsorship of the Rational Foundation for Infantile Paralysis and the University of Michigan.

Dr. Francis declared the vaccine had produced "an extremely successful effect" among bulbar-patients in the areas where vaccine and an inert substance had been tried interchangeably.

Financed by nearly one million dollars worth of dimes which have been donated to the National Foundation, the Francis Report may slow down what has become a double-time march of disease to a snail's pace.

In strong statistical language the historic trial of a vaccine and its subsequent analysis was revealed. Over 113 pages in length, the Report at long last called a halt to speculations and
finally re-enforced laboratory findings with concrete field evidence. There can be no doubt now that children can be inoculated successfully against polio.

There can be no doubt that humanity can pull itself up from its own bootstraps and protect its children from the insidious invasion of ultramicroscopic disease.

For one thing what was feared turned out to be unfounded -- the vaccine proved incredibly safe. Reactions were nearly negligible. Only 0.4 percent of the vaccinated children suffered minor reactions. An even smaller percent (0.004-0.006) suffered so-called "major reactions."

And the persistence of protection appears reasonably good. When good antibody responses were obtained from vaccination, the report said "the effect was maintained with but moderate decline after five months."

Distribution of antibody levels among vaccinated persons was much higher than that in the control population from the same areas.

Out of a total population of 1,829,916 children a total of 1013 cases of polio developed during the study period and were reported to the Center.

In placebo control areas, where vaccine was interchanged with an inert substance, 428 out of 749,236 children contracted the disease.

In the observed control areas where only second graders were inoculated, 585 cases out of 1,080,680 children developed.

Percentages in the placebo areas were: 67.5 paralytic, 17.6 non-paralytic, 7.2 doubtful, and 7.6 not polio. Specifically, 33 inoculated children receiving the complete vaccination series became paralyzed in the placebo areas. This is opposed to 115 uninoculated children. Similarly, in the observed areas there were 38 such children who became paralyzed, as opposed to 330 uninoculated children.

There were four deaths among children who received placebo; none among the vaccinated.
In observed areas there were 11 fatalities; none among children receiving the vaccine.

Only one child who had been inoculated with the vaccine died of polio, and this death followed a tonsillectomy two days after the second injection of the vaccine in an area where polio was already prevalent.

The Report also stated that in no area did Type II virus prevail. There was, however, prevalence in certain areas of Types I and III.

Marked sociological differences were noted by the U-M's Survey Research Center among the participating and non-participating children in the study. For example, there was a higher proportion of children participating who had been vaccinated against small-pox, diphtheria, and whooping cough than among the non-participants. Significant auxiliary findings were:

1. The vaccine's effectiveness was more clearly seen when measured against the more severe cases of the disease;
2. Although data were limited, findings in Canada and Finland support the Report in showing a significant effect of the vaccine among cases from whom virus was isolated
3. Vaccination protected against family exposure. Only 1 out of 233 inoculated children developed the disease, while 8 out of 244 children receiving placebo contracted the disease from family contact.
4. In picking the field trial areas, the National Foundation scored a major victory. Although in placebo areas cases were 27 per cent under the 1949-53 average, and 12 per cent less in the observed control areas, it was found that there had been a 26 per cent increase per 100,000 in trial areas as a non-trial areas. This meant that trial areas were appropriately selected for the best testing conditions for the vaccine.

The field trials and the evaluation were made possible by grants totaling $7,500,000 in March of Dimes Funds from the National Foundation for Infantile Paralysis.

http://www.sph.umich.edu/about/polioannouncement.html
Poliomyelitis has been around since ancient times. There is still no cure for the disease. But at the peak of its devastation in the United States, Jonas Salk introduced a way to prevent it.

This infectious viral disease attacks the nerve cells and sometimes the central nervous system, often causing muscle wasting and paralysis and even death. Since 1900 there had been cycles of epidemics, each seeming to get stronger and more disastrous. The disease, whose early symptoms are like the flu, struck mostly children, although adults, including Franklin Roosevelt, caught it too.

As a medical student and later a researcher at the University of Michigan, Salk studied viruses, such as influenza, and ways to vaccinate against them. Successful vaccines already existed for diseases such as smallpox. For each virus, a vaccine must be custom-made, but the principles are the same: if your body is exposed to a very weak or small amount of the disease virus, it will produce antibodies, chemicals to resist and kill the virus. Then when a full-strength version of the disease virus comes along, your body is prepared to fight it.

In 1947 Salk became head of the Virus Research Lab at the University of Pittsburgh. He began investigating the poliovirus. To start with, he had to sort the 125 strains of the virus. He found that they fell into three basic types and knew that a vaccine would have to include these three types to protect against all polio. One of the hardest things about working with poliovirus was manufacturing enough to experiment with—and to make vaccine production practical.

In 1948 researchers at Harvard (J.F. Enders, T.H. Weller, and F.C. Robbins) made a breakthrough with this. They found that the virus could grow on scraps of tissue, without needing an intact organism like a chick embryo. Bacteria usually contaminated the tissue, but Enders' team was now able to get penicillin—discovered 20 years earlier by Alexander Fleming and developed in the 1940s by Ernst Chain and Howard Florey—and prevent the bacterial growth. Now viruses like mumps or polio could be created in large quantities for study. This team won the 1954 Nobel Prize in physiology/medicine.

Now Salk could speed up his research. Using formaldehyde, he killed the polio virus but kept it intact enough to trigger the body's response. On July 2, 1952, Salk tried a refined vaccine on children who'd already had polio and recovered. After the vaccination, their antibodies increased. He then tried it on volunteers who had not had polio, including himself, his wife, and their children. The volunteers all produced antibodies, and none got sick.

In 1953 Salk reported his findings in The Journal of the American Medical Association. A nationwide testing of the vaccine was launched in April 1954 with the mass inoculation of school children. The results were amazing—60-70 percent prevention—and Salk was praised to the skies. But suddenly, some 200 cases of the disease were caused by the vaccine and 11 people died. All testing was halted. It seemed that people's hopes were dashed until investigators found that the disease-causing vaccine all came from one poorly
made batch at one drug company. Higher production standards were adopted and vaccinations resumed, with over 4 million given by August 1955. The impact was dramatic: In 1955 there were 28,985 cases of polio; in 1956, 14,647; in 1957, 5,894. By 1959, 90 other countries used Salk's vaccine.

Another researcher, Albert Sabin, didn't think Salk's killed-virus vaccine was strong enough. He wanted to mimic the real-life infection as much as possible; that meant using a weakened form of the live virus. He experimented with more than 9,000 monkeys and 100 chimpanzees before isolating a rare form of poliovirus that would reproduce in the intestinal tract but not in the central nervous system. In 1957 he was ready for human trials of an vaccine people could swallow, not get in a shot. It was tested in other countries, including the Soviet Union and Eastern Europe. In 1958 other researchers tested a strain in the U.S. and they tried to cast doubts on Sabin's "communist vaccine." In spite of this, his vaccine was licensed in 1962 and quickly became the vaccine of choice. It was cheaper to make and easier to take than Salk's injectable vaccine.

In the U.S., cases of polio are now extremely rare, and ironically, are almost always caused by the Sabin vaccine itself -- being live, the virus can mutate to a stronger form. Elsewhere there are still about 250,000 cases per year, mostly in developing nations where vaccination has not become widespread. The World Health Organization has goals to eradicate polio completely in the first decade of the twenty-first century.

http://www.pbs.org/wgbh/aso/databank/entries/dm52sa.html
The polio vaccine field trials of 1954, sponsored by the National Foundation for Infantile Paralysis (March of Dimes), are among the largest and most publicised clinical trials ever undertaken. Across the United States, 623,972 schoolchildren were injected with vaccine or placebo, and more than a million others participated as “observed” controls. The results, announced in 1955, showed good statistical evidence that Jonas Salk’s killed virus preparation was 80-90% effective in preventing paralytic poliomyelitis.

The statistical design used in this great experiment was singular, prompting criticism at the time and since. Eighty-four test areas in 11 states used the textbook model: in a randomised, blinded design all participating children in the first three grades of school (ages 6-9) received injections of either vaccine or placebo and were observed for evidence of the disease. But 127 test areas in 33 states used an “observed control” design: participating children in the second grade (ages 7-8) received injections of vaccine; no placebo was given, and children in all three grades were then observed for the duration of the polio “season.”

The use of the dual protocol illustrates both the power and the limitations of the randomised clinical trial to legitimate therapeutic claims. The placebo controlled trials were necessary to define the Salk vaccine—introduced by a lay organisation that has taken an activist position against the counsel of its virological advisers—as the product of scientific medicine. The observed control trials were essential to maintaining public support for the vaccine as the product of lay faith and investment in science. Here I examine the process by which the trial design was negotiated and the roles of the several actors.

Summary points
- The 1954 polio vaccine field trials used a singular statistical design
- Over 600,000 schoolchildren were injected with vaccine or placebo and over a million others participated as “observed” controls
- This dual protocol illustrates both the power and the limitations of randomised clinical trials to legitimate therapeutic claims

A Problematic Vaccine

On 23 January 1953, Jonas Salk of Pittsburgh presented the results of his tests of a “killed virus” polio vaccine on 161 children to the Immunization Committee, a scientific advisory committee to the National Foundation for Infantile Paralysis. The foundation, created in 1938 by President Roosevelt and his law partner, Basil O’Connor, was a lay governed organisation based on grassroots fundraising and volunteer effort. For 15 years a portion of the dimes and dollars collected in the annual “Mothers’ March” had been devoted to research: epidemiological studies of poliomyelitis, identification and classification of the three strains of the virus, development of practical culture methods. These projects had strong support among scientists, but for the foundation’s staff and volunteers they were necessary stepping stones to the development of an effective vaccine. Salk’s work seemed promising to O’Connor, and to Thomas Rivers, the dean of the foundation’s scientific advisers. The children had shown no ill effects and the levels of polio antibodies in their blood had risen. Almost immediately, O’Connor and Rivers began planning for a major field trial.

Several of the senior virologists on the Immunization Committee, notably the Nobel laureate
John Enders of Harvard and Albert Sabin of Cincinnati, thought these plans precipitate. They questioned the relation of antibodies to permanent immunity and doubted the safety of a vaccine prepared from virulent poliovirus, whatever “inactivation” method was used. Enders described Salk’s work as “most encouraging” but cautioned that “the ideal immunizing agent against any virus infection should consist of a living agent exhibiting a degree of virulence so low that it may be inoculated without risk” — that is, an attenuated strain that would create immunity by producing a subclinical case of the real disease, as in the classic cowpox/smallpox model.

Despite these objections, O’Connor believed that his organisation had a mandate from its volunteers and donors to proceed. As Harry Weaver, the foundation’s director of research, wrote: “The practice of medicine is based on calculated risk .... If [we wait until more] research is carried out, large numbers of human beings will develop poliomyelitis who might have been prevented from doing so.”

The virologists’ critique was only one obstacle to the field trial. Since paralytic polio was a disease of relatively low incidence, the experimental population would consist of school age children, the group with the highest case rate; the foundation decided to target the first three grades in the 272 counties with the highest incidence of the disease. Volunteers from the foundation would work through state and local health departments and schools to gain parental consent and deliver the children for injection. The use of a placebo control group seemed to be too much of a “calculated risk,” one that parents, teachers, and health officials would reject; in Salk’s words, “a ‘beautiful’ ... experiment over which the epidemiologist could become quite ecstatic but [which] would make the humanitarian shudder.”

The Foundation Enlists Support

On 9 November 1953, O’Connor announced that the field trials would begin in the spring and that an “observed control” plan would be used, in which one group of children would receive vaccine, while others in the same age group would not be injected but only observed. Hart Van Riper, the foundation’s medical director, asked the nation’s health officers for advice and support. Carrying the imprimatur of medical expertise, yet necessarily responsive to public fears, the health departments constituted a potential counterweight to the virology community.

Within a month, departments in 38 states had responded, most enthusiastic about the prospect of a vaccine and ready to use the observed control plan. A number of state officials, however, saw it as a problem that the project was sponsored not by scientists but by a lay organisation. They questioned the impartiality of an evaluation run by the foundation and the rigour of the proposed design.

To meet these objections, and those of the doubting virologists, O’Connor and Van Riper asked Thomas Francis of the University of Michigan to direct an independent evaluation of the trials, supported by funds from the foundation, but otherwise autonomous. Francis, a highly respected virologist who had conducted field trials of influenza vaccines, was supportive of the killed virus preparation. “I think I shall do it,” Francis admitted in a letter on 29 December; but before taking the job, he mobilised support among the state health officers to engineer a change in the trial design.

Two types of Controls

In a public statement on 8 January 1954, the foundation still adhered to the observed control
plan; but on 15 February, six days after Francis was formally appointed to head the evaluation, O’Connor announced that two types of controls would be used in the field trials: “observed controls” in 34 states and “placebo controls” in 11: “a combination of the two procedures [will] assure a valid evaluation of the trial vaccine.” This change in plans was the result of a month of manoeuvring on Francis’s part.

He had requested an “advisory group” meeting on 11 January. This new group was entirely distinct from the foundation’s scientific advisory committee, which was excluded from these deliberations. As well as the senior staff of the foundation, a selected list of state health officers, paediatricians, clinical polio specialists, statisticians, and virologists attended. Their charge was not to debate the merits of Salk’s work but to take the vaccine project from the laboratory into the field. Part of the January group later became an advisory committee for the field trial evaluation, and the state health officers constituted a separate body to advise on “technical aspects” of the project. Because the health officers were divided, Francis’s role was critical.

The 11 January meeting began with briefings from the foundation’s staff on plans to date. Rivers assured the group that the foundation would do its best to guarantee the safety of the vaccine. After general discussion, the group subdivided for the afternoon into three groups designated as “clinicians,” “statisticians,” and “health officers.” Though each of the groups made several recommendations, I will focus here only on their statements regarding trial design. The clinicians’ report assumed the use of observed controls, and the statisticians’ group, unsurprisingly, recommended the use of “a blind injected control” wherever the “proper facilities” made such a design possible.

Francis himself joined the “health officers” group. He listed in his notes several health departments that would support an injected, or placebo, control design: Massachusetts, New York, Michigan, Ohio, Illinois, California. Each was a populous state with a well organised health department headed by a nationally respected physician. Perhaps, he mused, a “double study” could be done in these states: placebo controls in the second grade, observed controls in the first and third grades.

Rewriting the Design

When the “health officers” met in the afternoon of 11 January, Francis found the group willing to endorse an even broader design. The participants included Francis, health officers from California, Illinois, New York, and Massachusetts, and two friendly virologists. Their report began emphatically: “It was the consensus of the group that [placebo controlled] studies were necessary ... that rather than limit the controlled study to the second grade it would be better to take the first three grades of school and select individuals ... on an alternate basis.”

The Health Officers’ Advisory Committee which met in Atlanta at the end of January was a select group of doctors from eight states who were supportive of placebo control. Francis told the group that he had decided to accept the job of directing the evaluation “with the understanding that a number of the states have indicated that they would like to, and would be able to, carry on injected [placebo] control studies.” The majority of the states, 36, preferred to adhere to the observed control design. Francis suggested that if a shortage of vaccine developed (which seemed quite likely at that point) supplies should be reserved for the placebo control areas; the group agreed with a formal recommendation that those areas be given “priority on available vaccine.” Someone asked whether the placebo control plan would make it more difficult to obtain the parents’ consent. The group decided that it could
rely on the widespread fear of the disease; members agreed that “it would not be difficult to sell as there is a high attack rate in the three grades [and] there would still be a 50% chance of a child receiving the vaccine.”

In Francis’s mind, the placebo control study was now his primary interest, and he reiterated this point in the summary report. Indeed, he seems to have stage managed the January meetings to reorient the project in that direction, selecting likely allies among the health officers and using their support to rewrite the trial design. “The best Departments are committed to this [placebo control] plan,” Francis told Van Riper. “The assurance and faith of those committed must be maintained.” Although it might be necessary to exploit parents’ fears to obtain their consent and to allow large numbers of children to face the polio season without protection, the use of a randomised and blinded controlled trial would effectively counter the criticisms of scientists such as Enders and Sabin, legitimise the sponsorship of the lay governed foundation, and gain the support of the leaders of the medical community, exemplified by the nation’s leading state health officers.

A National Event

But the observed control trials were not a sideshow to the main event, an unnecessary “deviation” from good methodology. Thirty six health departments, representing a large segment of public opinion and the rank and file of the medical profession, were committed to that plan and their participation was necessary to the field trial. If the Salk vaccine trials were to succeed, it was essential that they be a great national event, enlisting volunteers, doctors, and parents in one united effort that represented the culmination of 15 years of work and faith. Given the climate of scientific doubt that surrounded the killed-virus vaccine, it was essential that the field trials offer public, as well as scientific, validation of its effectiveness.

The National Foundation for Infantile Paralysis had tried to reconcile its scientific and political problems by working through the state health officers, but this group—each official facing the conflicting demands of professional training and public constituency—was itself divided. O’Connor then enlisted Francis and his impressive credentials, who, rather than pacify the advocates of placebo controls, chose to ally himself with them. The ensuing negotiations shaped a dual statistical design that reflected the multiple meanings of the trial: as scientific demonstration, political statement, and mass participation event.

“Polio pioneers”—some of the many children who took part in trials of poliomyelitis vaccine

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National Institutes of Health, Bethesda, MD 20892, Accepted October 6, 1998.