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THE 1954 SALK POLIOMYELITIS VACCINE FIELD TRIAL

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INTRODUCTION

On April 12, 1955, Thomas Francis, Jr., Professor of Epidemiology at the University of Michigan, held a press conference in Ann Arbor to announce the results of a “field trial” of an experimental poliomyelitis vaccine. “Some of the best-educated persons in American journalism” elbowed each other aside to get their hands on a copy of the press release. The journalists’ ardour was not surprising: more Americans knew about the vaccine trial “than knew the full name of the President of the United States” (Carter, 1966:268-273). The “biggest public health experiment ever” had enrolled 1,022,684 school children in 44 states.¹ 300,000 schoolteachers, “classroom mothers” and “clubwomen,” nurses, physical therapists, doctors, and public health officials had volunteered to organize the immunizations and track polio cases (Meier, 1975; Francis, 1957: xxix, 50-51). Around the country vaccine supplies were stockpiled, as families, physicians and government officials waited to hear whether the new vaccine had worked. Francis’ announcement that the vaccine was “80 to 90 per cent effective against paralytic poliomyelitis” did not satisfy Jonas Salk, the vaccine’s inventor, who promised future results of “100 per cent” effectiveness (Laurence, 1955; Carter, 1966: 242-244, 260-265, 274-278).

No medical study, before or since, approaches the 1954 Salk vaccine field trial in size, complexity, or the extent of public involvement. The trial was initiated not

by the federal government but by a private organization, the National Foundation for Infantile Paralysis (NFIP), which raised its money from millions of small donations. Ordinary citizens paid for the study, recruited the children who took the vaccine and the volunteers who helped administer it. Small wonder that trialists and vaccine researchers look back admiringly, even longingly, at the study (Dawson, 2004; Monto, 1999; Meier, 1990; John, 2004). Yet the most remarkable fact about the 1954 field trial may not be the massive organizational effort involved, or the rigorous methodological design ultimately imposed. Given repeated controversies about the vaccine's safety and the field trial's design, it is remarkable that the trial was ever begun, much less successfully completed.

The sciences of vaccine testing and of clinical trials are complex. Add parents, physicians, school and health officials from 3100+ communities and the process grows even messier, little resembling the orderly procedure the textbooks prescribe. In Pittsburgh, Jonas Salk continued modifying the test vaccine until a few months before the study was launched. The field trial itself was shaped by decisions taken not only in New York at the NFIP's headquarters, or in Francis' Ann Arbor, but in places like Montgomery, Alabama, where local health and school officials decided to go ahead with the trial, and Arlington, Virginia, where the community decided against participation. Capturing the difficulties trial organizers faced, the contingencies they encountered along the way and the actions taken to overcome these are the principal objectives of this chapter.

BACKGROUND

At the end of the nineteenth century, physicians began reporting outbreaks of a puzzling disease. Children would go to bed with a mild fever, perhaps complaining of feeling “ill”. They would awake in the morning partially paralyzed. In some cases, the paralysis proved fatal when the children could no longer breathe unassisted. Repeated epidemic outbreaks in Sweden in the 1880s were followed by outbreaks in Vermont (1894), New York (1907) and elsewhere in the United States. In 1916, there were 27,000 cases and 6,000 reported deaths in the United States, with 8,900 cases and 2,400 deaths in New York City alone (Paul, 1971: 71-87; Rogers, 1992). Thereafter, the threat of polio returned regularly to haunt the summers of middle-class children, who were less likely than the poor to have contracted a mild, non-paralytic infection at a younger age (Melnick & Ledinko, 1951; Smith, 1990: 155-159).

In 1934 and 1935, public health researchers in New York and Philadelphia began testing polio vaccines. The attenuated live-virus preparation (Philadelphia) was indicted for causing ten paralytic cases and five deaths among more than 10,000 inoculees, while sponsors of New York’s killed-virus preparation ordered the laboratory to stop human use after reports of anaphylactic reactions to the vaccine. Though the researchers—William H Park and Maurice Brodie (New York) and John Kolmer (Philadelphia)--denied that their vaccines had caused any injuries, for the

next twenty years virologists would remember how hastily they had proceeded to human testing and distribution of their vaccines. Any proposed vaccine had to pass through the gauntlet of these memories (Halpern, 2004: 49-63, 69-73).

Nonetheless, a series of technical advances after World War II made it possible to think of developing a safer polio vaccine, notably John Enders' and Thomas Weller's development of tissue culture methods allowing large-scale production of poliovirus in non-nervous tissue (Paul, 1971: 308-323; Benison, 1967: 226-319).²

By the early 1950s multiple researchers were experimenting with polio vaccines, among them the University of Pittsburgh's Jonas Salk. Like most polio researchers, Salk was funded by the NFIP which, unlike foundations founded by wealthy industrialists, depended on the contributions raised via its annual "March of Dimes" campaign. Begun in 1938 by Basil O'Connor, President Franklin Roosevelt's former law partner, the NFIP operated via a loosely federated network of lay volunteers. Local chapters conducted public education, cared for polio victims, and organized the annual fund-raising which paid for all these activities (Sills, 1957; Oshinsky, 2005: 43-91). Like the thousands who contributed their nickels, dimes and dollars, NFIP officials were committed to "unlock[ing] the door to victory over infantile paralysis." (Paul, 1971: 319; Brandt, 1978). While some NFIP-funded basic research ultimately proved crucial to vaccine development and testing, it did nothing in the short run to reduce suffering. The prospect of "victory" made NFIP organizers especially eager to find out whether Salk's vaccine worked.

PLANNING

Between 1951 and 1953, Salk's vaccine had to face a series of hurdles imposed by the eminent virologists on the advisory committees of the NFIP, each of them more experienced than Salk, who had only begun working on polio two years earlier, in 1949.³ Would the antibodies produced by a killed-virus vaccine translate into real and enduring protection against paralytic polio? Was the vaccine equally potent against the several strains of poliovirus? What proof had Salk that his vaccine contained not a single living virus? Was Salk sure that vaccine prepared from monkey kidney tissue would not cause organ damage in humans? Could Salk use a less virulent strain of Type I poliovirus and still achieve protection? (Carter, 1966: 122-155; Benison, 1967: 494-502; Paul, 1954). As Yale University's John Rodman Paul put it, the contemporary risk of paralytic polio was a "good deal less" than "1 in 500. Obviously it is essential that the risk of serious or other accidents occurring as a direct or indirect effect of the vaccination should be far less than 1 in a 1000" (Paul, 1954: 142).

Through much of 1953, both the testing and the vaccine itself remained works in progress (See figure 1). In response to his critics, Jonas Salk continued to test and refine his vaccine in successive populations: ninety-eight children at the D.T. Watson Home for Crippled Children, sixty-three children at the Polk State School, and eventually, several thousand children in Allegheny County (Salk, 1953; Benison, 1967:

507-509, 512-515). Salk's most vocal critic in these months was Albert Sabin, who was developing a competing live vaccine. Both at national scientific meetings and before the US Congress, Sabin raised questions about the safety and enduring efficacy of Salk's killed virus vaccine: "To give the impression that everything has been done that needs to be done prior to a large scale test is misleading" (Sabin, 1953b: 848; Sabin, 1953a). The majority of virologists on the NFIP's advisory committee were equally, if more discretely, concerned. They expected "that progress in the laboratory would proceed in the usual manner—without undue haste, without the use of large numbers of vaccinees, and especially without wide publicity" (Paul, 1971: 419, 419-424).

The virologists advising the NFIP expected testing of the Salk vaccine to follow a standard path, beginning with a handful of children, and progressing to tests on several hundred, all the while collecting detailed data about antibody responses to the vaccine. NFIP's O'Connor was not so patient. In consultation with his director of research, O'Connor decided to "break the logjam" created by its painstaking but painfully slow scientific advisors. In May, 1953, he created a committee of national authorities in public health to advise the NFIP on a field trial of the Salk vaccine. While the virologists continued to provide technical advice, they no longer called the shots (Carter, 1966:175-176).

Meanwhile, Harry Weaver, NFIP's director of research, had already begun thinking about a large field trial of Salk's vaccine (Benison, 1967: 506). Over the next

eleven months, NFIP officers faced two problems in planning a trial. The first was that Jonas Salk, in response to concerns about the safety and potency of his vaccine, continued to modify the vaccine and the protocols used to test it. It was one thing to produce a vaccine for research use, another to scale up production to inoculate several hundred thousand children. Salk's research laboratory could not possibly produce the vaccine in the necessary amounts, and NFIP enlisted several drug companies to supply the field trial. Parke-Davis, Eli Lilly and Connaught Laboratories in Toronto began producing the vaccine on an industrial scale. Yet Salk continued to be involved in negotiations over the protocols for the production and safety testing of the vaccine: must each lot be tested for residual live virus and if so, how many times and for how long? (Oshinsky, 2005: 191-193; Carter, 1966: 196-199; Benison, 1967: 514-515) Some changes were made against Salk's strong opposition—William Workman of the National Institutes of Health's (NIH) Bureau of Biologics (BoB) insisted that merthiolate be added to neutralize any bacterial contaminants, which according to Salk weakened the vaccine's potency against Type I poliovirus (Carter, 1966: 208-211). Legally, BoB approval was not required prior to licensing for commercial use but NFIP officials were not prepared to inoculate thousands of children without BoB's tacit endorsement. Each change in vaccine production had the potential to cause new problems: as late as March, 1954, some companies were reporting apparent residual live virus in their vaccine, although many of these "problems" turned out to be artifacts or due to a company's failure to follow protocols precisely (Benison, 1967:

512-516, 522-527, 529-534).

The second contested issue concerned trial design. Weaver had recruited Joseph Bell from the U.S. Public Health Service (PHS) to run the trials. Bell had been doing innovative controlled vaccine trials since 1938. His 1948 dissertation on pertussis vaccine evaluations was literally a textbook in how to design, operate and analyze such trials (Chalmers, 2006). For methodological and ethical reasons, Bell advocated a randomized positive-control trial, in which the control group received an injection of influenza vaccine. Active controls, Bell insisted, were the only way to ensure the credibility of claims made for the vaccine; giving the control group a proven vaccine rather than a saline injection was an added benefit in Bell's view. Salk disagreed: any injection, much less an active vaccine, had the potential to cause injury. Moreover, administering a control injection to so many children would consume valuable resources to no useful end. He advocated recruiting children in grades one and three as observed controls, while giving the test vaccine to second graders. Basil O'Connor, NFIP's director, sided with Salk and Bell returned to the PHS on October 31, 1953 (Benison, 1967: 509-511; Carter, 1966: 176-178, 182-194).

Polio is a warm-weather disease and this knowledge gave some urgency to the planning: a vaccine cannot reasonably be tested once polio has made its appearance in a community. After Bell's departure, NFIP's medical director began talking with Thomas Francis, Jr., Professor of Epidemiology at the University of Michigan. The Rockefeller-trained Francis had a distinguished career in vaccine and

influenza virus research; he was both well known and widely respected. That Jonas Salk had trained with Francis may have seemed an additional asset (Rogers, 1993; Carter, 1966: 28-53). Like Bell, Francis was adamant about a double-masked trial with randomized controls, but where Bell had proposed giving control subjects an influenza vaccine, Francis opted for use of a saline injection. After a month's negotiations, the NFIP gave in, with Salk's blessing. With other candidate vaccines in the works, they feared that if Salk's vaccine did not have its field trial in the coming summer's polio season, it never would: "everybody and his aunt would be trying out their own vaccines if the Public Health Service did not put a muzzle on them." (Benison, 1967: 511-512, 534-536; Carter, 1966: 202-206).

Previous historical accounts have emphasized Francis' crucial role in the decision to conduct a randomized, placebo-controlled trial. While there is no denying either his scientific integrity or his influence, agreement between Francis and the NFIP alone could not secure the design of a trial involving physicians, local and state health and school officials, parents and community groups across the country. The trial's design was negotiated and renegotiated over a period of approximately five months, from mid-November, 1953 through April, 1954. Throughout that period, state health epidemiology officers were discussing the design and organization of the study, in consultation with NFIP and with Francis (Report, 1953; Advisory Committee, 1954a). The support of local health officials was ultimately crucial to the adoption of a randomized design, but that support was neither automatic nor

uniform.

The NFIP had begun planning early in 1953, using its extensive network of local chapters to recruit potential subjects and volunteer labor for a field trial with observational controls. News late in the year that NFIP was considering a placebo controlled study came as an unwelcome surprise to local health officials. As Indiana's state health commissioner Leroy Burney explained:

“The parents of Indiana have indicated a willingness to cooperate in the original field trials by consenting that their children be immunized. Under the placebo plan, it might require considerable selling of the proposal for the child to receive three injections of an aqueous material as well as furnishing blood samples” (Burney, 1954).

Health officials in Arkansas, Connecticut, Delaware, Florida, Iowa, New Jersey, South Carolina, Virginia and the District of Columbia agreed: whatever the scientific merits of the randomized design, communities, parents, school officials and physicians had been “sold” on a study with observed controls, and it would be difficult to renegotiate those plans in time for the rapidly looming polio season (Herron, 1954; Osborne, 1954; Hudson, 1954; Sowder, 1954, Zimmr, 1954; Bergsma, 1954; McDaniel, 1954; Shanholtz, 1954; Seckinger, 1954).⁴ Vermont's state health commissioner did not understand all the fuss: “I somewhat question the necessity of a placebo program since all you are really testing is the effectiveness of a vaccine and either the kids get polio or they don't” (Aiken, 1954). In Kansas, health officials split the difference:

“The inhabitants [of Johnson county] are accustomed to the indiosyncrasies of research investogators [sic]” and could be enlisted for a placebo controlled study. A second county would stick with observational controls (Hoods, 1954).

Officials in other states, notably Illinois, Maryland, and New York, felt just as strongly that they would not participate in a field trial *unless* they could have placebo controls. The possibilities for bias in the observed control design were simply too great (Cross, 1953, 1954; Riley, 1954; Korn, 1954). As Herman Hilleboe, New York State’s commissioner of health noted, in 1953 polio had, by chance, attacked far fewer second graders than children in the first or third grades. Had the latter groups been used for comparison in a field trial, one would have mistakenly credited the vaccine with achieving a reduced rate among those second-graders (Hilleboe, 1953) . Hilleboe, who had previously trained and worked with advocates of clinical trials (e.g. Johns Hopkins’ Margaret Merrell and Carroll Palmer), made the participation of his prestigious and large health department contingent upon a placebo-controlled trial (Hilleboe, 1968: 3, 12; Hilleboe, 1964). In meetings with Francis and NFIP officials, other state officials committed their efforts for a randomized study (Report, 1953; van Riper, 1954; Gill, 1954). The result was a compromise, with some locations opting for a randomized, placebo-controlled study, and the remainder relying on observational controls.

Study design aside, the other major concern in the winter of 1953-1954 remained vaccine safety. The safety testing protocols were a complex affair,

involving the federal BoB, the NFIP, Salk and the drug manufacturers. State officials in Illinois, Maryland, Massachusetts and Minnesota indicated that they could make no final commitment to participate until they knew more of the details about the safety testing (Cross, 1953; Riley, 1954; Feemster, 1954; Kirkwood, 1954; Chesley, 1954). In Ann Arbor, Francis fielded multiple queries from around the country about the vaccine's safety (Oshinsky, 2005: 193-194). Then, a few weeks before the field trial was to begin, Walter Winchell broadcast the news that the "new vaccine" soon to be given to a million children "may be a killer." Seven of ten recently-tested lots, Winchell reported, had contained "live (not dead) polio virus" and had "killed several monkeys" (Carter, 1966: 231-232). Although the viral particles were found through BoB's process for screening vaccine lots, Winchell's announcement on April 4, 1954 crystallized existing anxieties in medical circles about Salk's vaccine (Carter, 1967: 231-232; Benison, 1967: 516-522; Hailey, 1954; Francis, 1954abc). Michigan withdrew from the planned trial, only to re-join shortly thereafter. State health authorities in Minnesota and various local health authorities around the country decided against participating.⁵ A Vermont reporter wired the Surgeon-General for reassurances that the vaccine was safe, and that Burlington children were in "no sense being used as 'guinea pigs'" (Sullivan, 1954). Only public statements by the Public Health Service and a blue-ribbon of virologists that the vaccine was safe allowed the trial to proceed (Carter, 1966: 232-237). Nonetheless, the Winchell broadcast had a lasting effect: in Michigan, Arkansas and Ohio, participation rates in the trial were down by 35% to

51% (Advisory Committee, 1954c). Francis later estimated that Winchell had discouraged 150,000 children from participating (Advisory Committee, 1954b).

DESIGN

The final design of the field trial incorporated two distinct studies, differently designed and separately analyzed. In eleven states, 455,474 first, second and third-graders were randomized by blocks of ten within each classroom to receive either a series of three vaccine or three placebo injections.⁶ New York State alone provided nearly half (226,381) of the children enrolled in the randomized study; Alabama, California, Illinois, Iowa, Massachusetts, Michigan, Montana, Ohio, Utah and Washington contributed the remainder (Francis, 1957: 2, 354-355). As Thomas Francis emphasized, “the nature of the material administered was concealed in a code,” so that “all observations and records regarding these children would thus be made on an objective basis: bias between vaccinated and controls was thereby eliminated” (Francis, 1957: 32). An additional 567,210 children from thirty-three states participated in a study with observational controls: 221,998 second-graders received the three successive vaccine doses; children from the first and third grades in these areas served as controls (Francis, 1957: 3, 356-359).

Francis had far less confidence in this observational study. From past experience, Francis knew that children from working class backgrounds were more likely to have developed antibodies from naturally acquired polio infections. The

investigators would have no way of knowing if such children would be over-represented among the observational controls, diluting any comparison between the control and experimental groups. Control subjects in these areas were not the same age as the experimental group, and since they also included those “unwilling” to participate, “variations in susceptibility and cooperation cannot be estimated.” Since everyone would know which children had received the vaccine, “bias, even though unintentional, could be introduced at each stage of diagnosis and observation of cases” (Francis, 1957: 31).

Francis’ concerns over bias are understandable, given the number and variety of end-points contemplated. Cases of paralytic and non-paralytic polio in the study areas had to be reported and confirmed. Additional antibody studies were performed as well on a sample of participants, to measure the vaccine’s effects against each of the major poliovirus strains. If medical personnel knew which children had received vaccine, they might well scrutinize those individuals more intensively.

Polio was neither a very common disease nor was it easy to diagnose. Participating counties had to be both willing and able to participate: thus, small areas (population under 50,000) were generally excluded because the “public health and medical resources required were less readily available.” Eligible areas were ultimately selected on the basis of high attack rates in recent years, analysis having found that this was the best predictor of a “good” attack rate in 1954 (Francis, 1957: 29-30).⁷ Local officials and medical societies were not the only ones who had to be

persuaded. The most crucial volunteers were the parents who offered up their children as experimental material.

NFIP officials were at pains to avoid describing the field trials as an experiment. Rather they presented the study as an opportunity. As historian David Oshinsky observes, participating children

“were called ‘polio pioneers.’ On the parental consent form, the standard phrase ‘I give my permission’ was changed to ‘I hereby request,’ implying that not every child would be fortunate enough to be picked (Oshinsky, 2005: 190-191; Carter, 1966: 229-230).”

In New York City, parents hoped that their children were receiving “the real vaccine,” even though the “consent” form in these placebo-controlled districts stated that half the children would be getting an innocuous saline injection (Time, 1954). The most difficult “consents” to obtain were from the parents in the observational control areas, allowing investigators to take blood samples from a random sample of children in the control group (Dublin, 1954; Cleere, 1954; Weigele, 1954).

CONDUCT PHASE

On April 26, 1954, six-year old Randy Kerr of McLean, Virginia received the first injection: “It hurt less than a penicillin shot,” he reported (Oshinsky, 2005: 197). Fairfax County’s health officer, Harold Kennedy, had held over sixty meetings to explain the trial’s details to concerned parents. His efforts were successful, with 2,335

second-graders from northern Virginia joining Randy in receiving the vaccine (Daub, 1993-94: 13-16) Around the country, NFIP volunteers had organized to recruit participants. In Montgomery, Alabama they vowed to “round up [children] along the creek banks, on the sandlots or wherever they are (Time, 1954).” In Lexington, Kentucky, mothers “tramped over hills and backroads” in a rainstorm to get permission slips signed for students who had arrived without them (Oshinsky, 2005: 197-198). Once the children were assembled, twelve pages of instructions choreographed each step with military precision: Clerk # 4

“lines children up in groups of ten. First ten in alphabet forms line on right; second ten in alphabet forms line on left; third ten in alphabet forms line on right. Prepares children for the shots. Has children take off coats and bares arm. Children in right line bares left arm and children in left line bares right arm” (Instructions).

In New York City, volunteers packed up “21,058 syringes, 381,000 sterile gauze bandages, [and] 25,917 gauze vials” for delivery to the schools, where 2500 volunteers assisted several hundred doctor-nurse teams in delivering the shots (NYC, 1954a; Baumgartner, 1954). The correspondent visiting a school in “a sorry neighborhood of tenements” on the Lower East Side had the rationale for performing random antibody tests explained to him in exquisite detail by a volunteering mother:

“Some of the children may already have had one or more of the three kinds of polio virus without knowing it, and thus be immune to one or more of them,

and it's important in computing the success of the Trials to estimate the frequency of such cases." (New Yorker, 1954).

By the end of June, 626,779 children around the country had received the full series of three inoculations (Francis, 1957: 37). The NFIP's central office was in charge of distributing vaccines, producing training materials and other directives, recruiting medical and nursing volunteers to help with vaccination and follow-up, and keeping a huge army of volunteer labor on track. As the summer wore on, Francis' Evaluation Center played an increasing role in managing case follow-up and reporting problems, assisted by epidemiologists from state health departments and the Centers for Disease Control (Francis, 1957: 35-36, 78).

In a study as large and as complex as the 1954 field trials, it would be remarkable if everything went according to plan. The organizers had planned on a study population of 1.8M children. 613,738 children initially "enrolled" in the study either failed to show up or had their consent withdrawn; consent forms could not be found for another 193,494 children (Francis, 1957: 2-3).⁸ In other cases, children were sent home for their consent forms. Some children moved after their first inoculation and had to be tracked down, while yet others (3.9%) never showed up to complete the full series (Francis, 1957: 2-3).⁹ An NFIP volunteer in one district refused to provide the names of children whose parents refused participation, as they did not deserve "the distinction of a listing in Francis' files." Some records arrived late and some not at all: in Davenport, Iowa, one school's vaccination records simply

disappeared. Such operational glitches were predictable and, in most cases, remediable by Francis' coordinating center (Oshinsky, 2005: 197-198; Carter, 239-241; Francis, 1957: 39-67). Jonas Salk was concerned over vaccine lots whose potency against Type I polio had been compromised by the use of merthiolate (Carter, 1966: 241-242). Others worried about the "liberal use of gamma globulin" injections by physicians and health officers, which might artificially lower polio incidence in some study areas (Kennedy, 1954; Ridge, 1954; Francis, 1954d).

The field study's most serious challenge was in determining just how many cases of polio there were. *Any* case of polio, "paralytic, nonparalytic, suspect or doubtful" occurring in a study area was to be reported by local physicians and/or health officers. Migrants and children in out-of-area summer camps had to be tracked down (Francis, 1957: 83-85). Most cases (>86%) were admitted to hospital, where physical examinations were performed by physicians and by specially trained physical therapists, and blood and stool samples obtained. Discharged patients were re-evaluated by a physical therapist 50-70 days later. These clinical evaluations were reviewed by a physician "especially skilled in the clinical aspect of poliomyelitis," while any fatal cases were to be autopsied. All these evaluations were performed by individuals ignorant of the child's vaccination status (Francis, 1957; 76-82).

Despite considerable efforts at standardization, variations in these clinical assessments arose. To resolve the numerous uncertainties--was this a case of poliomyelitis or not, and if so, of what severity?--a small group of specialists redid the

classification scheme and reviewed many of the individual diagnoses during the analysis phase (Francis, 1957: 86-89; Francis, 1954f).

ANALYSIS

As in any large trial, reports were slow in trickling into the coordinating center. On August 30, 1954, there were still 160,000 records missing (Francis, 1954e; Voigt, 1954). In early October, 800 New York children were asked to come in for repeat antibody tests: “Ten ccs of blood is a little less than one tablespoon and as the children now know, it is taken easily and painlessly” (NYC, 1954b). Data collection continued through the fall; complete records on suspected polio cases were still coming in that winter (Francis, 1954g; Michigan University, 1955: 8). By January, 1955 it seemed increasingly doubtful that the report on Salk’s vaccine could be released before the new polio season was imminent: “There would be little time for scholarly rumination by the medical profession or virologists or epidemiologists or the National Institutes of Health” (Carter, 1966: 255-256). Still, NFIP’s O’Connor kept his promise to allow Francis full control, including deciding when the analysis was complete.

On April 12, 1955, the methodic Francis presented his report to a room packed with journalists and scientists. The executive summary had not yet been invented: one has to hunt through the 113 page report for the two tables summarizing the results. In the “experimental” areas there were 57 cases of polio (28/100,000) in the

vaccinated group versus 142 cases (71/100,000) in the group receiving a placebo. Results in the “observed” areas pointed in the same direction, 56 cases (25/100,000) among the vaccinated versus 391 cases (54/100,000) among the observed controls. In both the experimental and observed areas, poliomyelitic severity increased in the control group: all fifteen fatal cases, for example, were in the control groups (Michigan University, 1955: 22-27).¹⁰

Aided by press releases from the University of Michigan, newspapers around the country announced a clear and simple verdict: “Salk Polio Vaccine Proves Success;” “Polio Conquered;” “Triumph Over Polio” (Laurence, 1955; Chicago Daily Tribune, 1955a; Washington Post, 1955). Medical scientists at the conference heard a more complex message: there was, Francis insisted, no “single value” for measuring the vaccine’s effectiveness. Estimates of effectiveness varied, depending on whether they were taken from the observed or the experimental areas, which outcome measures one emphasized (paralytic vs. non-paralytic polio; all cases vs. laboratory-confirmed cases), which vaccine lots were used in a given locale, and what kind of poliovirus strains one worried about. For the handful of cases (85) where virus was recovered, it appeared that the vaccine’s effectiveness against the commonest poliovirus strain (Type I) was 68% as compared to 100% against Type II and 92% against Type III (Michigan University, 1955: 49-50). For reasons never fully explained, polio rates among six year olds enrolled in the study did not show the protective effects seen in seven eight and nine year olds. (Michigan University, 1955:

17-18).¹¹ The considerable detail about epidemiology, serology and vaccine lots were of tremendous importance to virologists planning the next vaccine. The overall message to the public was far simpler: “There is no longer any ambiguity or uncertainty about the efficacy of the Salk polio vaccine (Washington Post, 1955).”

IMPACT

The immediate impact of the field trial was to generate unprecedented demand for the vaccine. On the evening of April 12, William Workman of the BoB met with a group of virologists in Ann Arbor to discuss federal licensing of the vaccine. The previous July, O’Connor had gambled \$9m to underwrite vaccine production, and more than 10 million doses were stockpiled. Should they be released? After two hours discussion, Workman phoned the Surgeon-General. His advisors unanimously recommended licensure (Carter, 1966: 281-282). Newspapers reports of the field trial results the following day were accompanied by articles announcing local plans to distribute the vaccine (Haseltine, 1955; Chicago Daily Tribune, 1955bc; New York Times, 1955). It was the quickest federal approval on record.

The NFIP had attempted without success to get federal authorities to plan for an equitable and organized distribution of the vaccine. On April 13, manufacturers began delivering the vaccine. While politicians debated whether to underwrite a national vaccination program, and local health authorities wondered how to pay for vaccine, a new problem emerged (Chicago Daily Tribune, 1955d; Asbury, 1955;

Carter, 1966: 301-308; Oshinsky, 2005: 216-221). On April 25 and April 26, Workman's office was informed that children in Illinois and California who had received polio vaccine were partially or completely paralyzed (Offit, 2005: 65-68). One manufacturer—Cutter Laboratories—voluntarily suspended vaccine distribution. Over the next month, manufacturers, federal authorities and virologists attempted to determine what had gone wrong and to devise new protocols for production and safety testing. Meanwhile, vaccine distribution was either suspended or in extremely low gear, as manufacturers tried to adjust to the new requirements. The final toll on the “Cutter incident,” as it is known, included 200 or more cases of vaccine-related polio, the resignation of multiple senior federal officials, and a substantial reduction in public confidence in the new vaccine, evidenced in the lowered than expected immunization rates that year.¹²

Francis had pronounced the polio vaccine safe as well as effective but the newly approved vaccine was not the same as that used in the field trials (Michigan University, 1955; 18-21). The protocols for producing and testing the vaccine had been modified many times since the lots produced for the field trials, most notably by the removal of merthiolate preservative. Prior to licensing, federal authorities had sought a guarantee that the modified vaccine was safe, but as Jonas Salk wrote Workman in January, 1955, none of the existing laboratory protocols for safety testing could be “construed as an adequate ‘safety test’” for the newer vaccine: “if a safety test is to be done it must be done in hundreds of thousands of children and,

preferably, with a placebo control” (Salk, 1955). Salk’s suggestion, possibly facetious, that another field trial be done was never taken up. Protocols for polio vaccine safety testing continued to be revised (and criticized) over the next several years (Cornfield, 1956; Federal Register, 1956, 1957, 1958).

Possibly the greatest impacts of the trial were indirect, having to do with the vaccine as much as with its evaluation. The publicity around the trial not only made Jonas Salk a national hero, it greatly cemented public support for medical research more generally. And in the wake of the Cutter incident, federal authorities strengthened protocols for vaccine safety testing, while its role in tracking down the victims of contaminated vaccine gave a substantial boost to the prestige of the Centers for Disease Control’s Epidemiological Intelligence Service (Etheridge, 1992: 73-80).

The impact of the 1954 field trials in the longer run is harder to determine. Statisticians were quick to celebrate Francis’ study (Cochran, 195?; Eisenhart, 1960). Johns Hopkins’ William Cochran thought Francis had established “a vital principle for future studies...that no loophole for bias should be permitted.... The advantage in having a blind placebo lies not merely in giving greater validity to the conclusions. It removes worries and uncertainties at many stages in the analysis (Cochran, 195?).”¹³ Francis’ design and management of the 1954 field trial were certainly prescient, but was it influential? The subsequent Soviet tests of Albert Sabin’s attenuated live poliovirus vaccine were massive but uncontrolled (Horstmann, 1991). Trials of other

vaccines followed the more usual practices of incremental testing on several hundred children at a time (Stokes, 1962). The credit for introducing masked evaluations with randomized controls must go to earlier evaluations of pertussis vaccine by Joseph Bell (1941) and the British Medical Research Council (1951) [Chalmers, 2006; Jefferson, 2006]. In any case, well-controlled vaccine trials appear to have been the exception, not the rule, well into the 1960s (e.g. Guinee, 1966).

Yet memory of the study was preserved among those close to it like the statistician Paul Meier, who wrote several articles celebrating the 1954 field trial (Meier, 1975; 1990). For younger researchers accustomed to conflicts over therapeutic studies, the trial's massive participation stood as an exemplar of what American volunteerism could achieve, while others celebrated Thomas Francis' principled stand for randomization. Anniversaries produced additional accounts, making a new generation aware of the trial's achievements (Meldrum, 1998; Dawson, 2004; Rogers, 1993; Oshinsky, 2005). There are certain aspects of the 1954 field trial one would not like to repeat: the "last-minute" approach to vaccine design or the extensive incorporation of observed controls.¹⁴ As David Byar recognized in trials of HIV treatment, lay participation in planning can be inconvenient, but it can bring a knowledge and passion which are otherwise hard to find (Harrington, 1998). Certainly, the process by which each community decided the terms of its participation gives new meaning to the term "consent". And as Leona Baumgartner, New York City's Health Commissioner, observed of some public school children

involved in the 1954 field trial:

“These youngsters [gave] as good a description of a controlled experiment as I’ve ever heard. I was very excited, because it seemed to me that if you could teach a generation of kids about what a controlled experiment was, and about what science really was, this was a plus value regardless of whether the vaccine was any good or not” (Dawson, 2004: 127).

That is not a bad legacy to remember!

Figure 1. Chronology of Key Events

Fall, 1951	Jonas Salk produces immunity in monkeys
May, 1952	Salk begins testing polio vaccine on institutionalized children
May, 1953	Basil O'Connor (NFIP) creates Vaccine Advisory Committee.
Summer, 1953	Joseph Bell hired from PHS to direct field trial
October 31, 1953	Bell returns to PHS after disagreements re his proposal for a trial with active, randomized controls
Nov, 1953-Jan 1954	Salk and others revising specifications for vaccine
December 5, 1953	NFIP meets with Thomas Francis to discuss field trial evaluation
Dec 14-15, 1953	State epidemiologists begin meeting with NFIP to discuss participation, field trial design
January 25, 1954	NFIP agrees to Francis' terms for an autonomous evaluation incorporating double-masked placebo trial of vaccine
February 23, 1954	Salk begins field testing vaccine on 5,000 Pittsburgh-area schoolchildren
April 4, 1954	Walter Winchell announces vaccine "may be a killer"
April 25, 1954	NFIP Vaccine Advisory Committee pronounces field trial vaccine "safe"; PHS endorses decision to start trial
April 26, 1954	Field trial inoculations begin in McLean, Virginia.
June, 1954	Field trial inoculations completed.
June-July, 1954	O'Connor commits \$9m to drug companies to purchase vaccine for 1955 polio season
June-August, 1954	Follow-up of polio cases in field trial areas
July-Dec, 1954	Data collection, editing
April 12, 1955	Francis announces field trial results. Federal Bureau of Biologics licenses vaccine.
April 13, 1955	Manufacturers begin vaccine distribution.
April 25/26, 1955	Bureau of Biologics informed of polio cases in children receiving vaccine

- April 27, 1955 Surgeon-General Leonard Scheele requests Cutter Laboratories recall all lots of its vaccine.
- May 6, 1955 Surgeon-General requests that all companies stop vaccine distribution
- May 14, 1955 Surgeon-General authorizes resumption of vaccine distribution
- April, 1957 Francis issues final report of Vaccine Evaluation Center

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¹ The larger figure of 1,829,916 children is sometimes quoted; this includes roughly 800,000 children whose parents did not provide consent or whose consents were lost. Polio cases occurring in these populations were nonetheless tracked (Francis, 1957: xxix, 50-51).

² The second key innovation: the development of methods for rapid typing of poliovirus strains, used in diagnosis. The third element was Isabel Morgan's demonstration that formalin-inactivated virus could prevent polio in monkeys.

³ Salk's earlier work had been on influenza vaccines, done under Tommy Francis' aegis in the 1940s (Carter, 1966: 45-53).

⁴ Officials in various other states declined to participate in the placebo controlled study without elaborating on their reasons.

⁵ Among the withdrawals were Arlington County (Virginia), Winnebago County (Illinois), East Baton Rouge (Louisiana), Washtenaw County (Michigan). The prolonged controversy in the Spring of 1954 meant that additional areas, including the states of Maryland, Georgia and North Carolina were unable to get distribution organized prior to the onset of the polio season (New York Times, 1954a, 1954b, 1954c; Chicago Daily Tribune, 1954; Jordan, 1954; Washington Post, 1954ab).

⁶ As each vial contained 10cc of injectable material (vaccine or placebo), children were randomized in blocks of ten. (Michigan University, 1955: 4-5; Francis, 1957: 55-56).

⁷ See also Carter (1966: 229), who notes that some spectacular fund-raising NFIP chapters could not be included because their polio levels were not high enough.

⁸ Polio cases were nonetheless tracked in these children, though not included in the principal analysis.

⁹ This rate includes vaccinated and placebo subjects in the experimental areas who failed to complete the full series, as well as vaccinated subjects in the observed study who did not receive all three injections. An additional 50,432 either withdrew their permission or never turned up.

¹⁰ These numbers exclude some 150 reported cases across both studies which were determined not to be polio.

¹¹ That is, the rates for six year olds enrolled in the study were roughly equivalent to those seen in their communities, whereas the older children had lower rates than the

local incident rate that year.

¹² There is no fully adequate account of safety testing for the Salk vaccine before and after the field trials. Most accounts, then as now, are as concerned with assessing blame as with analyzing the socio-technical processes involved in such testing. “Safety” is both a product of the technical performance of various screening tests and of the resource implications of specific testing protocols (how many times and for how long must each vaccine lot be tested). The best account at present is Offit (2005). See also Meier (1957); USPHS (1955).

¹³ Compare Brownlee (1955), who was highly critical of including the observational areas.

¹⁴ Monto (1999) and Burke (2004) raise additional concerns about the sample size calculations and the end-points initially chosen.