CHAPTER II

# ORGANIZATION OF THE 1954 FIELD TRIAL *

## BACKGROUND AND PERSPECTIVES

Early in 1953 Salk reported that a formalin-treated virus vaccine, prepared in his laboratory, had produced neutralizing antibodies against all three types of poliomeylitis virus in children who possessed no demonstrable circulating antibodies against these viruses before vaccination.[41]

This trivalent vaccine appeared to be noninfectious; inoculation of human subjects was free of untoward reactions. Moreover, the method of inactivation with formalin, developed at the University of Pittsburgh Virus Research Laboratory, appeared to provide a wide margin of safety in dissociating virus infectivity from its antigenic properties. Inactivation proceeded as a first order chemical reaction, thus permitting ready standardization and rigid control. Experiments in progress gave promise of the early development of even better antigens, capable of inducing persistently high levels of neutralizing antibodies comparable to those observed in individuals who had experienced naturally occurring infection and clinically recognized disease.

Immediately following publication of this report, a distinguished group, aware of the social as well as the scientific implications of these observations, concluded that only a meticulous and systematic extension of Salk's work could adequately determine the effectiveness of the experimental vaccine under conditions of epidemic exposure. The recommendations of this group, supported by editorial comment in the Journal of the American Medical Association on April 4, 1953, were set forth in an open letter to the medical profession, signed by Dr. Thomas M. Rivers, Director of the Hospital of the Rockefeller Institute for Medical Research.[22,37] The step-by-step plan and timetable outlined in this letter provided the guide lines adhered to by the National Foundation for Infantile Paralysis in the Field Trial of the vaccine.

In advance of the 1953 season, Salk had administered the vaccine to approximately 600 individuals, of whom 474 were children between the ages of four and twelve. None contracted clinical poliomyelitis during the season of observation; 7 were known to have been exposed to the disease through intimate contact; 3 of these 7 may be presumed to have been infected since they showed a subsequent rise in circulating antibody titers.[40]

Salk's observations followed closely upon other notable advances in the understanding of the pathogenesis and immunology of poliomyelitis. In 1949, Bodian, Howe, and Morgan established the existence of at least three distinct types of poliomyelitis virus.[7] Soon thereafter cooperative research in four different university laboratories confirmed these findings and established their epidemiological significance. This typing program, sponsored by the National Foundation, suggested that efforts to control poliomyelitis by immunological means need be concerned only with the three varieties of the virus that had been isolated from human infections.[13]

Concurrently, in 1949, Enders and his associates demonstrated that the poliomyelitis virus could be propagated in cultures of nonnervous tissue.[17] This supported the hypothesis that the virus might multiply elsewhere in the body before reaching the central nervous system and provided a technic which could be adapted to the mass production of virus necessary for large scale manufacture of the vaccine.

* The material included in this chapter concerning the activities of the National Foundation for Infantile Paralysis in planning and organizing the vaccination program was largely provided by Dr. Thomas D. Dublin, Medical Consultant, Vaccine Division, NFIP.[15]

## ORGANIZATION OF THE FIELD TRIAL

In 1952, Horstmann and Bodian independently found poliomyelitis virus circulating in the blood of experimental primates for a brief period during the prodromal stage of disease, thus indicating a possible site for the establishment of an immunological barrier to the paralytic sequel of infection.[5,6,21] In the following year, Hammon established that poliomyelitis antibodies, passively transferred to human subjects by inoculations of gamma globulin, temporarily enhanced protection against the paralytic form of the disease.[20]

These fruitful explorations led medical authorities serving on National Foundation advisory committees to recommend, in the fall of 1953, that an extensive field trial of the vaccine developed by Dr. Salk be conducted. In the past, certain vaccines and immunizing agents had been introduced into general use without substantial evidence of effectiveness. Some, even after years of popular acceptance, have failed to demonstrate measurable evidence of efficacy. Others, through trial and error and the expenditure of considerable time, effort, and money, had been modified and improved and had gradually established their usefulness in the prevention of acute communicable diseases. It was assumed that with the resources of NFIP and with the widespread public concern for those afflicted with poliomyelitis a field trial applying modern methods of clinical, immunological, and epidemiological study could with unprecedented speed establish answers to many questions:

1. Could the vaccine prepared in the research laboratory be reproduced consistently and uniformly by commercial manufacturers?

2. Would neutralizing antibodies induced by the vaccine protect susceptible individuals against the paralytic forms of the disease under natural conditions of exposure?

3. Would mass use be attended by untoward reactions comparable to the dangers of the disease itself?

4. If the vaccine was protective would the immunity induced by it be complete or partial?

5. Would the strains of virus used in this vaccine induce protection against all strains responsible for the naturally occurring disease?

6. Are the comparatively few individuals who develop paralytic poliomyelitis through natural exposure those who do not respond readily to artificial immunization?

Many additional questions were raised, but it was apparent that none could be conclusively answered without crucial studies conducted on a scale sufficient to obtain statistically valid evidence. Some would require long-term study; for example, the duration of protection. Most questions, however, seemed capable of answer within a one-year undertaking.

The following objectives were, therefore, established for the Field Trial:

1. To determine whether a formalin inactivated trivalent poliomyelitis vaccine would afford protection against naturally occurring paralytic poliomyelitis in selected groups of children during the poliomyelitis season next following vaccination; and if protection is provided, the degree of such protection.

2. To determine what, if any, levels of actively induced antibodies are associated with subsequent resistance to paralytic disease.

3. To observe the nature and incidence of untoward reactions to the vaccine.

In mid-November, 1953, the National Foundation announced that the Field Trial would be initiated prior to the 1954 poliomyelitis season and that vaccination would begin in February.

The program, under the over-all supervision of Dr. Hart E. Van Riper, Medical Director, National Foundation for Infantile Paralysis, was to be guided by advisory

groups drawn from the National Foundation's own committees on research and professional education and by other committees designated by the Association of the State and Territorial Health Officers.

Three phases were established for the Field Trial. The first concerned the planning of the entire operation and included the preparation, by cooperating manufacturers of biological products, of the large amount of vaccine that was needed. This phase began to accelerate in the summer of 1953 and continued beyond the actual start of inoculations in the field in late April, 1954. The Connaught Laboratories of the University of Toronto were enlisted to develop mass production methods for the cultivation of virus in high concentrations by using monkey-kidney tissue culture technics.

A group of American manufacturers, with extensive experience in the preparation of vaccines, were then recruited to undertake inactivation of the virus and actual production of the vaccine. Five such manufacturers agreed to participate on a nonprofit basis in this phase of the program. Two, Parke, Davis and Company of Detroit and Eli Lilly and Company of Indianapolis, succeeded in overcoming the many production problems and in meeting the rigid safety requirements in time to permit the use of their vaccine in the actual Field Trial.

The second, or Operational Phase, of the Field Trial gained momentum in the early fall of 1953 and reached a maximum of intensity in late April, May, and June, 1954, when inoculations were given. Technically speaking, the third, or Evaluation Phase, might be considered as beginning with the submission of completed reports to the Evaluation Center. However, no sharp line can be drawn between field operations and evaluation. The National Foundation coordinated field activities during the vaccination phase of the program, including the distribution of vaccine and placebo and the requisite supplies and forms to the schools, and arranged for the necessary local volunteers to assist the teachers and doctors in the numerous vaccination clinics held for each of the three inoculations during the spring of 1954. The Poliomyelitis Vaccine Evaluation Center assumed responsibility for the designing of record forms, for the collection and processing of all records of the involved population including participants and nonparticipants, and for the follow-up of the children taking part in the Trial. In addition, it directed the collection and collation of case reports and other data essential to the evaluation.

# SCOPE OF STUDY

## FACTORS DETERMINING SCOPE

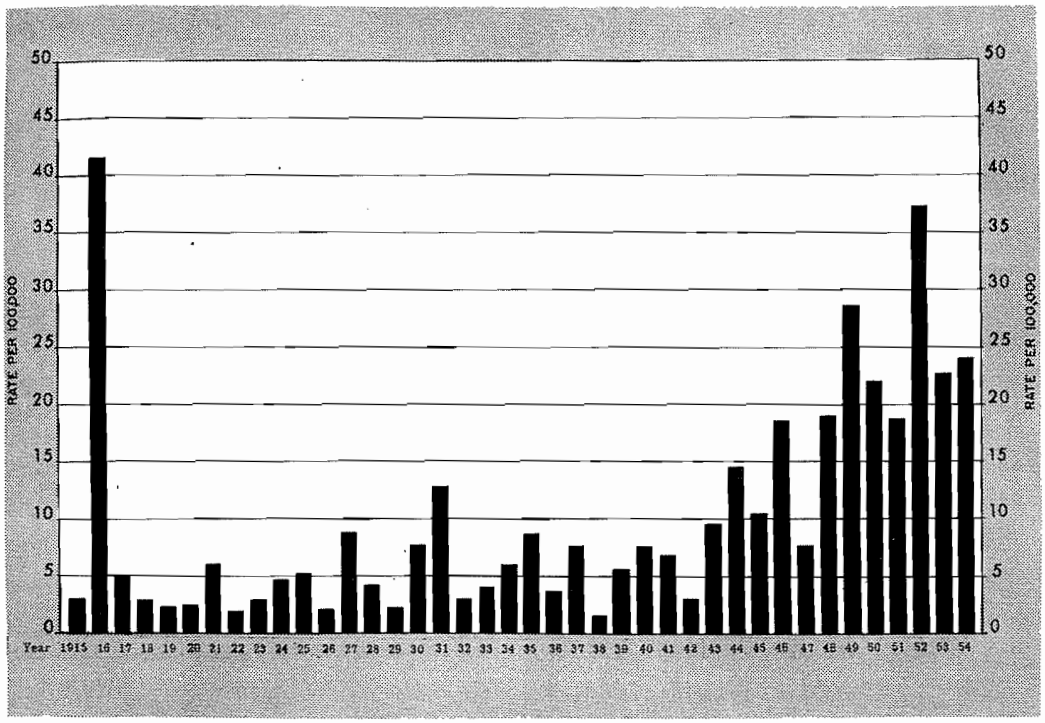
### Geographic Requirements

From the earliest considerations of a field trial, it was recognized that a study of considerable size would be necessary if the effectiveness of the vaccine was to be measured. As is well known, the risk of clinical poliomyelitis has been extremely small as compared with many other disease entities. During the ten-year period 1943-1952, national poliomyelitis case rates averaged only 18.5 per 100,000 population. Moreover, during the last fifteen years the variation in incidence in the United States has ranged from a low of 3.1 in 1942 to a high of 37.2 in 1952 (Figure 2). The unpredictability of epidemic poliomyelitis in a community in any given year is also well-recognized.

Because of these and other known epidemiological characteristics of the disease, a decision was reached by the National Foundation for Infantile Paralysis to conduct the Field Trial on a nationwide basis, provided the cooperation and assistance of state and local authorities and of the public could be obtained. Communities would be selected according to geographic and socio-economic factors so as to provide a cross section of the United States population. It was also agreed that preference would be given to communities where the maximum number of cases might be anticipated for the study year and to those communities where health and educational resources would permit satisfactory conduct of of the Trial.

Figure 2

REPORTED POLIOMYELITIS CASES PER 100,000 POPULATION*
UNITED STATES, 1915-1954



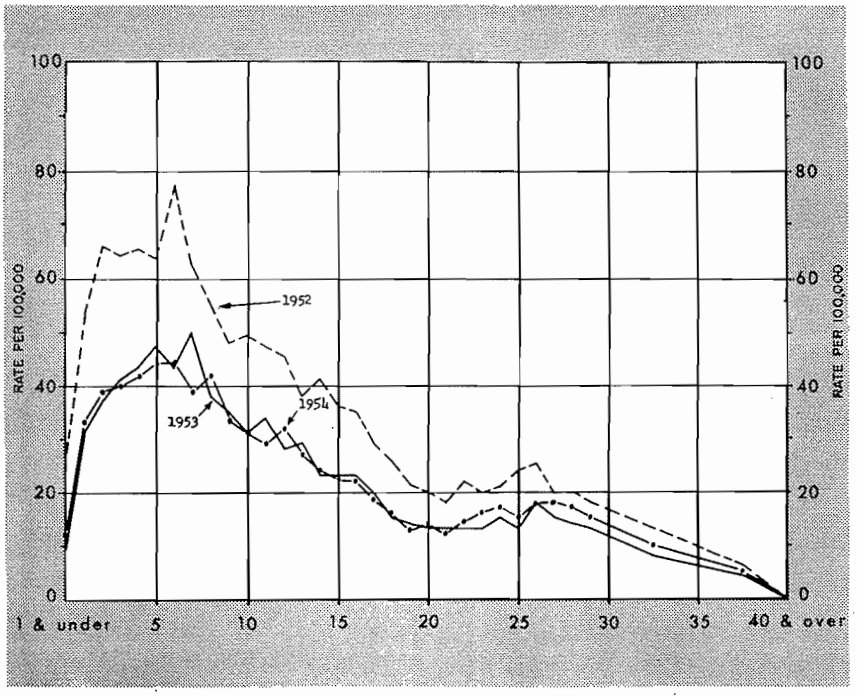

* Mid-year population estimated by Bureau of the Census.
SOURCE: U. S. Public Health Service.

## Age Factors

Since no reliable prediction of poliomyelitis incidence in the study population during the study period could be made, it was imperative that the composition and size of the study group enhance the probability of statistically valid observations. Although the distribution of poliomyelitis has changed in the United States in recent years, it remains essentially a childhood disease. Almost 75 percent of reported cases occur in persons under twenty, and over 50 percent in children under ten. The peak ages of clinically diagnosed poliomyelitis occur in the years immediately before and after entrance into primary school (see Figure 3). This fact and the accessibility of school children in organized groups for vaccination determined the selection of children enrolled in the first three grades of primary school as the study population. Enrollment in these classes roughly corresponds with the age band six through nine in which, on a national basis, at least one out of five of all reported cases might be expected to occur.

Figure 3

POLIOMYELITIS AGE-SPECIFIC ACUTE ADMISSION RATES
PER 100,000 POPULATION,* 1952,** 1953,† 1954††




* Mid-1952, 1953, and 1954 population estimate.
** 1952 rates based on 35,882 notices of original acute admissions in 1952 received July 20, 1952, - January 31, 1953.
† 1953 rates based on 23,698 notices of original acute admissions received January-December.
†† 1954 rates based on 24,950 notices of original acute admissions received January-December.

Number of Children Required for Study

To determine the degree of effectiveness of vaccine in preventing poliomyelitis was the purpose of the study, but the size of the needed population would be governed by the effect.

It was possible, nevertheless, utilizing the annual incidence rates of reported poliomyelitis for the United States and theoretical assumptions of degree of vaccine effectiveness, to estimate the probable minimum size of the study population required to give statistically authoritative results. Based on such analyses, it could be anticipated that if in the Field Trial areas a low incidence rate of paralytic poliomyelitis were encountered and the vaccine were only 50 percent effective, it might be necessary to vaccinate almost 700,000 children and observe an equal number of controls before valid findings could be obtained. If, on the other hand, the vaccine should prove 80 percent or more effective and an "average" poliomyelitis year should occur, a high level of certainty of the results could be derived from a study of fewer than 100,000 subjects divided equally between vaccinated and controls. A conservative approach dictated that a practical goal be set for the inoculation of between 500,000 and a million children.

Other Factors

A variety of other factors had a restrictive effect on the scope of the study. The plan adopted by the Advisory Committee of the Foundation required that each child receiving vaccine be given a series of three 1-cc. injections intramuscularly at 0, 1, and 5 weeks. The amount of vaccine which would be available could be estimated only from production and processing schedules of the manufacturers. They were subject to change, but in any event the amount of available vaccine would be limited. The use of three doses created a further limitation to the number of children who could be vaccinated. Moreover, it was almost mandatory that the vaccination schedule be completed while the schools were still in session, with the result that only the vaccine available within a limited period of time could be used. It was evident, also, that the three-dose schedule would increase the administrative and technical detail and thus influence area-participation.

## SELECTION OF FIELD TRIAL AREAS

Earlier studies[19] cast doubt upon the possibility of selecting specific areas which might be expected to experience epidemic conditions during the Field Trial. On the other hand, the observations of Benjamin and Logan in England and Wales[3] offered encouragement that a group of areas with high prevalence in the past might yield higher-than-average attack rates in a subsequent year. In a report presented at the American Statistical Association, Stickle[46] confirmed these findings in studying poliomyelitis incidence in the more than 3,100 counties in the United States.

Summarizing Stickle's findings, it became apparent that counties with a population of 50,000 to 200,000 experienced a significantly higher average annual attack rate than those with a population of over 200,000. Although the recorded incidence of reported poliomyelitis is usually somewhat higher in counties with populations under 50,000, it was necessary, in general, to omit these smaller jurisdictions from further consideration since public health and medical resources required for the Trial were less readily available in the smaller areas. Further analyses indicated that intercounty variability in case rates was more than three times that of year-to-year variance within counties, and that counties with the highest average attack rates over a 5-year period have, in the aggregate, a substantially higher-than-average attack rate one or two years later.

Table 16

POLIOMYELITIS CRUDE CASE RATES BY SIZE OF COUNTY, 1948-1952

| Population Class (Thousands) | Number of Counties | Total Population 1950 (Millions) | Poliomyelitis Cases, 1948-1952 | | |
|---|---|---|---|---|---|
| | | | Total Number | Average Annual Number | Average Annual Rate Per 100,000 |
| All Counties - Total | 3,103* | 150.7 | 189,072 | 37,814 | 25.1 |
| Under 50 | 2,608 | 47.6 | 65,289 | 13,058 | 27.4 |
| 50 and Over | 493** | 102.7 | 123,783 | 24,757 | 24.1 |
| 50 but less than 200 | 377 | 35.1 | 46,033 | 9,207 | 26.2 |
| 200 and Over | 116** | 67.5 | 77,750 | 15,550 | 23.0 |

* Includes 3,070 counties, 29 independent cities, the District of Columbia, and parts of Yellowstone Park, in Idaho, Montana, and Wyoming.
** Excludes Norfolk City and Richmond City, Virginia.

On the basis of such analyses, it seemed justified to recommend the participation of those counties of 50,000 to 200,000 population reporting the highest average attack rates during the five-year interval 1948-1952, the latest period for which data were available. This preliminary method of selection did not exclude some larger and some smaller counties where it seemed both desirable and feasible to include them. In the extensive discussions which followed, several supplementary criteria for selection were developed. For example, preference was given to areas with well-organized health services capable of conducting effectively the operational and follow-up phases of the Field Trial, and where the interest and cooperation of local health and school authorities and the willingness of parents to request participation of their children were manifest. One additional criterion was important in the final selection of Field Trial communities. Areas experiencing significant outbreaks before the start of inoculations were to be excluded. This was considered desirable in order to avoid, as far as possible, any fortuitous association of inoculations with the onset of cases.

The final result of these considerations was the joint selection by the National Foundation and state health officers of the 211 areas in 44 states. Actually 217 areas, or health jurisdictions, were designated, some of which were combined for tabulation purposes where a county and a large central city had separate health authorities (see list in Chapter III). Before inoculations were begun in late April, 1954, the number of areas expected to participate was somewhat larger. However, Maryland, Arizona, and the District of Columbia withdrew because of inability to complete the inoculation program prior to the closing of schools. All three Field Trial areas in Georgia were excluded at the last moment because of the occurrence of cases of paralytic poliomyelitis in the period immediately preceding inoculations. Minnesota authorities failed to sanction the program within that state in time to permit the necessary preparations.

Because of interest in the program outside of the United States and the desire to add as many trial areas as time and materials would permit, 46 areas in three Canadian provinces, Alberta, Manitoba, and Nova Scotia, took part in the Trial; two small areas in Finland also were included.

In 1954, the areas included in the Field Trial in the United States experienced a reported case rate of 28.1 per 100,000 population which was 22 percent higher than the rate in non-trial areas. Thus, the criteria for the selection of participating trial areas actually fulfilled expectations in maximizing the number of cases in the test population.

## PLANS OF STUDY

Between early December, 1953, when the request was first made and mid-January, 1954, when the decision was reached to accept the proposal to form the Vaccine Evaluation Center at the University of Michigan, the needs, the commitments already made, and the feasible approaches were carefully reviewed. From the outset it was evident that the program contained many known variables, each with its own biological complexities; these and other potential variables would have to be taken into account in the plan of study if mathematically precise results were to be obtained. It was recognized that the accuracy of measurement would be dependent on the tightness of controls, the degree of strict comparability between the test group and the controls, the size of the numbers involved, the true effectiveness of the material under test, the uniformity of procedure in collection and compilation of the data and the objectivity of the interpretation of the results.

The proposed Field Trial of poliomyelitis vaccine was confronted by uncertainty in many respects. It was not a laboratory experiment involving fixed parameters even though the objectives were clear. The size of the population could not be established until the amount of vaccine available was known and the number of volunteering participants was determined. There was a sound experimental immunological basis for expecting a measurable effect of vaccine but this was completely in-

ferential and the uniformity of the product was unknown. Even the clinical diagnosis of paralytic poliomyelitis is not of uniform accuracy especially in the milder cases; if only severe cases were to be considered much important information could be lost. The prime purpose of the Field Trial was to provide a firm basis for measurement of the effect of the vaccine in large scale use, regardless of whether the determined effectiveness was found to be little or large, favorable or unfavorable.

Plans for investigations of the projected scope of the Field Trial in human populations cannot usually meet all the ideal and theoretical requirements of strict statistical procedure; rather, they commonly represent compromises with practicable, workable considerations. Outstanding effects have been demonstrated in medical fields through procedures controlled only by a well-established expectancy based upon a uniform experience of mortality or other sharply defined characteristics. Observations of this nature have, however, more commonly resulted in unconfirmable impressions. Moreover, well-controlled studies, relatively precise within the limits of human ability to conform to an agreement, could be conducted on a sizeable scale as shown by the investigations of vaccination against influenza and pertussis. Regardless of the plan to be followed in the Field Trial of poliomyelitis vaccine, the element of selection would be present. The population concerned was to be selected from the age groups with the highest expectancy of poliomyelitis but only from those in the first three grades of participating schools. There was further selection in that only those who volunteered would receive vaccine.

## THE OBSERVED CONTROL PLAN

The plan proposed by the National Foundation for Infantile Paralysis and endorsed by a number of states, was to vaccinate those children of the second grade whose parents requested participation while all children of the corresponding first and third grades were to be kept under observation as the control group. The procedure poses difficulties to objectivity: all field observers could readily determine whether a child had received vaccine, and bias, even though unintentional, could be introduced at each stage of diagnosis and observation of cases. The ages of the vaccinated and unvaccinated do not correspond although they overlap. Those who were vaccinated were active participants while the control group included those willing to participate as well as the unwilling; such an arrangement contains opportunity for bias due to variations in susceptibility and cooperation which cannot be estimated and would thus limit the reliability of results. The adequacy of this plan would depend upon a high incidence, a high degree of effectiveness of vaccine, and the completeness of case reporting in the unvaccinated population.

The purpose of the Field Trial was not to prove that the vaccine was protective but rather to measure the effect, if any, of an untried product. It constituted in reality a test of an immunological hypothesis and current concepts of pathogenesis of poliomyelitis. Proper data could speed the progress of scientific research toward improvement if beneficial results were noted, or toward reconsideration of accepted theories and redirection of research if negative results were obtained. A more definitive plan of procedure was necessary if data which would permit firm conclusions as to effect were to be obtained.

## THE PLACEBO CONTROL PLAN

A second study plan was introduced as a requisite of the Evaluation Center. It conformed in pattern to that employed in well-designed scientific investigations, providing strict comparability between the control and test groups. The children were all those in the first three grades of school whose parents requested their participation with knowledge that the children would receive injections of unidentified material. Students were to be divided at random within each classroom; one half would receive vaccine, the other matching half would receive a solution of similar appearance and composition except that it contained no inactivated virus or tissue products and should have no influence on immunity to poliomyelitis. Each child would receive three inoculations from one lot of material.

The nature of the material administered was concealed in a code, the key to which was kept only at the Evaluation Center. All observations and records regarding these children would thus be made on an objective, concealed basis without knowledge of the inoculum received; bias between vaccinated and controls was thereby eliminated. These two equivalent halves of the participating group constituted the experimental population in the placebo areas. Those who refused to participate and received no inoculations, and the biases which might accompany them, were thus removed from consideration; they are not additional controls any more than children from non-study areas would be. This is emphasized because some reviewers of the April 1955 Summary Report have apparently had difficulty in recognizing this basic scientific principle.

The operative procedures involved in this, the placebo control study, required considerably more effort and attention. Because of its greater soundness and reliability, however, epidemiologists of several well-populated states had already expressed a preference for such a procedure and indicated their willingness to engage in the study on that basis. The placebo study was conducted in 84 areas of 11 states with 200,745 vaccinated and 201,229 placebo controls. The total first, second, and third grade populations of these areas was 749,236. At one time it appeared that nearly all the vaccine could be used in placebo control areas but the delays and uncertainties reduced the available numbers. Moreover, commitments had been made by the NFIP to other states which had organized their programs on the basis of observed controls and chose to proceed with them.

## PROVISION FOR THOROUGH REPORTING OF DATA

In observed areas where the group to be compared with the vaccinated comprised both those who would be willing to participate and those who would not, it was essential that the cases arising in dissenters not be missed or concealed. For this reason, and to secure uniform decisions regarding individual cases, it was decided that all cases occurring during the study period in members of the first, second, and third grades of the participating schools in all study areas would be reported and investigated in the same manner, and that concerted action would be taken to assure that every case would be detected. All paralytic, nonparalytic, suspect, and doubtful cases were to be reported and investigated. Similar emphasis was placed on reporting and follow-up of all cases in registered study members of the placebo study areas.

It was not possible in the time available before the start of the Field Trial for the Evaluation Center to develop a single organization which could undertake complete responsibility for each step of the operative procedure in all areas. Such an organization would presumably assure uniformity of procedure and performance but it would still be completely dependent upon strong local support. The operative plans were, therefore, based upon the active participation of the local health and medical professions and their affiliates. Extended efforts were made to acquaint the responsible administrative groups in each study area with the need for accuracy, uniformity, and completeness in performance and recording.

It was emphasized that each study area was a part of the coordinated study with the Vaccine Evaluation Center serving as the central agency to which all records would come for assimilation and analysis. As a condition of participation it was agreed that no preliminary estimates or reports would be made by local or state agencies until the Center had made a report of the total experience. The agreement was strictly honored throughout the study period.

## SOCIO-ECONOMIC CHARACTERISTICS PARTICIPANTS : NONPARTICIPANTS

In placebo areas the controls were firmly established; children whose parents specifically refused to let them receive inoculations were not to be considered as additional

controls. Similarly, children of the second grade of school in observed areas who were offered the vaccine but who did not receive it because their parents said, "No," could not properly be considered as additional controls. However, since reporting of cases arising in these "nonparticipants" was requested in both placebo and observed areas, it would be of value to know more about them in the event their epidemiological behavior differed from that of the participants. Furthermore, as previously discussed, the designated controls in observed areas included a mixture of participants and nonparticipants. Therefore, knowledge concerning characteristic differences between the participating and nonparticipating segments of the study population should aid in the interpretation of comparisons between the "mixed" observed controls and the actively participating vaccinated group.

A number of studies have indicated, moreover, that willingness to participate in activities such as the vaccine evaluation program is influenced by socio-economic factors. It was possible, therefore, that factors of this nature were involved in the decision as to whether or not parents requested participation of their children in the vaccine evaluation program, particularly in placebo areas where participation meant accepting the injection of an unknown substance, with a 50 percent chance of its being vaccine.

Data from numerous investigations have shown that infection with poliomyelitis virus occurs at an earlier age in the lower socio-economic groups.[2,18,50] Differences in willingness to participate in the study might thus reflect differences in susceptibility between the participants and nonparticipants.

Since the population under observation in placebo areas was well identified as to acceptance, it was particularly suited to investigation of similarities or differences in the other characteristics of the component groups. It was also agreed that the findings of such a study in the placebo areas would have general applicability to the characteristics of participants and nonparticipants in the observed study areas. It was decided, therefore, with concurrence of the VEC Advisory Committee, that a study to gain information of this nature was desirable so that significant variation between the characteristics of those who refused participation and those who requested it might be estimated beyond the known, fundamental difference in willingness to join in the study.

Accordingly, at the request of the Vaccine Evaluation Center, a survey of the socio-economic status, educational level, living conditions, and health consciousness of a sample of the total study population of placebo areas was undertaken by the Survey Research Center of the University of Michigan. It was conducted as a study of child health in ten of the eleven placebo control states.

The participating or nonparticipating members of this sample population were clearly identified in VEC files. Acceptance had meant full participation: furnishing samples of blood and receiving injections of an unknown substance, either vaccine or placebo. The demonstrated similarities in the composition of vaccine and placebo groups had already indicated that they were a single population of participants which could be studied and compared with the nonparticipating segment. The sample, composed of 1,300 carefully selected families, was representative of the total study population of the placebo areas.

The sample design was decided upon as a joint effort of the Survey Research Center and the Vaccine Evaluation Center in November, 1954. Of the 1,300 families selected, 1,102 were interviewed. Fifty-six of the families requested participation but did not follow through to actual participation. Data are presented for them, but comparisons are made only between the other two groups, participants and non-requests. The interviewers had no information of the participation status of the families; neither interviewers nor respondents were informed of the relation of the study to the Field Trial. The field interviewing was concluded in December, and the compilation and analyses were completed by the Survey Research Center during January and February, 1955. Funds for the project were

Table 17

SUMMARY OF SOCIO-ECONOMIC CHARACTERISTICS

| Socio-economic Characteristics | Percent of Total Sample | | Source of Data* |
|---|---|---|---|
| | Participants | Nonparticipants | Table No. |
| Family Income $4,500 or More | 58 | 40 | 4 |
| Father: Professional, Managerial, Clerical, or Sales | 41 | 26 | 3 |
| Neighborhood - Good | 37 | 24 | 5 |
| Homes - Good | 48 | 33 | 5 |
| Care of Home - Good | 49 | 36 | 5 |
| Vaccination: | | | |
| Smallpox | 87 | 80 | 6 |
| Whooping Cough | 88 | 78 | 6 |
| Diphtheria | 91 | 82 | 6 |
| High Confidence in Above Vaccinations | 68 | 55 | 7 |
| Mothers' Activities Outside Home: | | | |
| Two or More Evenings Per Week | 34 | 24 | 8 |
| P.T.A. | 36 | 27 | 8 |
| Informal Social | 36 | 51 | 8 |
| Mothers' Education: | | | |
| Grade School | 10 | 26 | 9 |
| Some High School | 23 | 29 | 9 |
| Complete High School | 49 | 36 | 9 |
| Some College or More | 17 | 7 | 9 |
| Number in Sample | 665 | 381 | - |

* Abstract from Report on the Child Health Study, see Appendix.

supplied by VEC from those appropriated by the NFIP to the University of Michigan evaluation program.

Table 17 presents proportions of participants and nonparticipants for each of the major socio-economic factors. The differences are significant at the 99 percent level of confidence except for vaccination for smallpox which differed at the 95 percent level.

1. A much smaller percentage of participants had family incomes under $4,500. Participation rate increased steadily with increasing income.

2. Fathers of participants were more likely to be engaged in middle class occupations (professional, managerial, clerical, and sales).

3. The interviewer's rating of the quality of the respondent's neighborhood and condition of his house was highly correlated with

participation status. Participants lived in better neighborhoods, and their homes were better kept.

4. The frequency of vaccination against smallpox, diphtheria, and whooping cough strongly correlated with participation.

5. Participants more frequently stated that "shots always work" than nonparticipants.

6. Mothers of participants were more likely to spend two or more evenings a week in outside activities than were mothers of nonparticipants.

7. Mothers of participants were more likely to have completed high school than mothers of nonparticipants.

An abstract of the Report on the Child Health Study may be found in the Appendix.[16]

The study revealed distinct and significant differences, demonstrating that those who refused to participate in the vaccination program do indeed differ sociologically from the participants. These demonstrated sociologic differences support the conclusion that the nonparticipants are also different immunologically and could, therefore, be expected epidemiologically to be more resistant to poliomyelitis than the participants. Moreover, the results establish further reasons why the refusals cannot be accepted as a group comparable with those receiving vaccine or placebo who are equivalent parts of a single population.

## DIVISION OF RESPONSIBILITY

It was apparent from the outset that large numbers of individuals with varying professional skills and other competences were needed if the test was to be successful. The majority of these individuals were volunteers recruited in the local Field Trial areas. It is estimated that more than 300,000 persons, including physicians, nurses, school teachers, public health and school officials, and community volunteers recruited by National Foundation chapters and by other civic, fraternal, or service organizations cooperated in this extraordinary medical undertaking.

Organization in each community centered around the schools where children who were to take part in the Field Trial were enrolled. Classroom teachers and volunteers shared responsibility for the schoolroom census and registration of the study population, the handling of parental request forms, the basic education and preparation of children and parents for the test, and the guidance of children to and from the vaccination clinics. For the most part, inoculation of children took place in school clinics. However, where the number in a given school was small, or where it was otherwise advantageous to do so, larger or more centralized clinics were held elsewhere in the community.

Coordination of activities in the schools was channeled through the school principal to the local health officer. In the absence of a health officer, a qualified practicing physician usually served as the director of the program. It was the responsibility of the director to enlist interest and support for the program, to recruit the necessary physicians and other professional staff, and, with the aid of volunteers supplied by the local chapter of the National Foundation, to attend to the infinite number of details required by the program.

The state health officer assumed over-all responsibility for the program in his jurisdiction. Participation in the Field Trial was, in general, decided after his consultation with state educational authorities, the state medical society, and such local groups in the prospective Field Trial areas as might be indicated. The state office staffs of the National Foundation and its regional representatives were placed at the disposal of state health departments to assist them in the many specialized tasks required. Though freedom to adapt the program to established local practices was permitted, officials of each state agreed that uniformity of procedures and forms would be maintained, that publicity regarding results of the vaccination study would not be made independently, and that

analysis of the data collected would be left exclusively to the Evaluation Center. There was understanding at all operational levels that publication of the results of the Trial would be made only by the Evaluation Center when, in the opinion of the staff of the Center and its advisors, such action would be justified.

Within the National Foundation itself, only a small coordinating staff was assembled, for the most part drawn from the various operating departments of the headquarters office. Under the direction of Dr. Hart E. Van Riper, this group served as staff for the various advisory committees of the Foundation and provided liaison with the laboratories and manufacturers engaged in the preparation of the vaccine. In addition, it collected and analyzed essential statistical data concerning distribution and use of vaccine, assisted state health departments in the selection and preparation of communities for field operations, and prepared educational and instructional materials for use in the field. Other departments of the National Foundation, particularly those dealing with its 3,100 local chapters and with public relations, were also intimately involved in the program. A major function of the National Foundation was to develop the interest and support of professional groups in the health and education fields, and of civic, fraternal, and service clubs.

## STANDARDIZATION OF PROCEDURES

So that each state and community taking part in the Field Trial would complete each step in a standardized manner, a Manual of Suggested Procedures was prepared.[27] Addressed primarily to the local health officer, the Manual outlined the basic principles and policies of the Field Trial, defined functions and responsibilities of those participating in it, and explained the procedures to be followed in each community. In addition, it described the record forms, educational materials, and supplies to be furnished by the National Foundation to each community. Supplements to the Manual, in the form of Operational Memoranda, were also prepared so that physicians in charge of vaccination clinics, school principals, classroom teachers, clinic recorders, and others would have available to them relatively brief check lists of their tasks and assignments.

As vaccinations proceeded, the Evaluation Center issued a series of memoranda specifying the manner in which all records were to be handled. These memoranda also outlined the steps to be followed in the identification, reporting, study and follow-up of illness occurring in members of the total study population. A regular channel of communication was maintained between the Center and the responsible health officers in each Field Trial area. Special effort was made to impress those with administrative responsibilities in the study areas with the need for completeness, accuracy, and uniformity of all records which were to be forwarded to the Center and which would ultimately provide the data essential to an objective appraisal of the vaccine.

## TIMETABLE AND SCHEDULE OF INOCULATIONS

Initially, the established timetable anticipated that inoculations in the field would begin in early February and continue through May with the program starting in southern states, where the seasonal rise of poliomyelitis usually appears first, and proceeding northward. It was clearly understood, however, that inoculations would not begin until (1) there were assurances that sufficient vaccine would be available to permit a reasonable measurement of its effectiveness; (2) safety and sterility tests of a predetermined and extensive nature had been carried out independently on each lot of vaccine in three laboratories: by the manufacturers, by Dr. Salk, and by Biologics Control of the National Institutes of Health; and (3) Dr. Salk had extended his preliminary pilot study to a minimum of 5,000 human subjects without harmful effects. In addition, the antigenicity of each lot of vaccine produced by manufacturers for use in the Field Trial would be

SCHEDULE OF INOCULATIONS BY VACCINATION CLINIC
PLACEBO AND OBSERVED AREAS

| Inoculation Status by Clinic | Total | Placebo Areas | Observed Areas |
|---|---|---|---|
| U. S. Study Population - Total | 1,829,916 | 749,236 | 1,080,680 |
| Completed Series of 3 Inoculations | 623,972 | 401,974 | 221,998 |
| Vaccine | 422,743 | 200,745 | 221,998 |
| Placebo | 201,229 | 201,229 | - |
| Inoculated at 1st Clinic | 650,864 | 419,009 | 231,855 |
| Vaccine | 441,058 | 209,203 | 231,855 |
| Placebo | 209,806 | 209,806 | - |
| Inoculated at 2nd Clinic | 642,471 | 413,169 | 229,302 |
| Vaccine | 434,354 | 205,052 | 229,302 |
| Placebo | 208,117 | 208,117 | - |
| Inoculated at 3rd Clinic | 626,779 | 404,520 | 222,259 |
| Vaccine | 425,550 | 203,291 | 222,259 |
| Placebo | 201,229 | 201,229 | - |
| Received 1 Inoculation or More | 650,937 | 419,035 | 231,902 |

titrated by Dr. Salk in comparison with the response he had obtained with material produced in his own laboratory.

These rigid though essential prerequisites, established by the Vaccine Advisory Committee of the National Foundation, were met on April 25, 1954. This Committee then recommended that the nationwide Field Trial proceed.[52] At that time, the U. S. Public Health Service made the following statement: "We believe that the judgment of the Vaccine Advisory Committee is sound and that the National Foundation for Infantile Paralysis is justified in proceeding according to the Committee's recommendations."

So that the medical profession would be kept fully informed concerning the background of the Field Trial and developments as they occurred, periodic releases were prepared for publication in national, state, and local medical journals. Shortly before the actual start of inoculations, each practicing physician in the country received through the mail a special reprint of an article on vaccination against poliomyelitis prepared by Dr. Van Riper.[53]

On April 26, 1954, the first of the series of inoculations was begun. Altogether, 650,864 individuals in the study population of 1,829,916 children in the United States received first inoculations. One week later 642,471 children began receiving second inoculations, and five weeks later 626,779, or 96.3 percent of those who had received the first dose, began to receive third inoculations.

While it was necessary that VEC maintain a timetable and schedule of clinical activities

in all study areas to administer inoculum and obtain blood specimens, it was also advisable that the Center retain a degree of fluidity in its directives to accommodate certain unusual circumstances that might arise. A few areas which had planned to participate in the Field Trial were compelled to withdraw because of a number of poliomyelitis cases locally reported at the outset. Several other counties such as Greene County, Missouri, and Davis County, Utah, were delayed in obtaining sanction for participation until after clinics were scheduled to begin; these areas were accepted at the later date, and clinics were set up for them shortly thereafter.

The entrance of Canada and Finland into the Field Trial was possible because of the later poliomyelitis season in those countries. Canadian clinics began inoculating during the period from May 24 through June 14. Finland was unable to put its program into effect until August. Schools were closed at that time, and the Finnish doctors and nurses were called upon to make trips out into the areas to inoculate the children. Consequently, the completion of the necessary first, second, and third inoculations and the receipt of data from these areas outside the United States were considerably delayed.

In observed control areas vaccine was given only to requesting children in the second grade. A complete series of three inoculations of vaccine was given to 221,998 persons. An additional 9,904 received an incomplete series of one or two inoculations of vaccine.