Chapter I

PLAN OF STUDY

Establishment of Study Population and Participants

Selection of Field Trial Areas: The selection of areas in which to carry out the field trials sought to meet the geographic peculiarities of poliomyelitis and to anticipate the areas in which the disease would be most prevalent. The National Foundation for Infantile Paralysis with extensive study had developed a basis for concluding that, in the aggregate, counties demonstrating consistently high reported poliomyelitis attack rates during the previous five year period were more likely to have attack rates in excess of the national average during the study period. The 100 counties with populations from 50,000 to 200,000, and with consistently the highest reported incidence of poliomyelitis 1946 through 1950, were observed to have an attack rate of 31 per 100,000 population in 1951 compared with a rate of 20 per 100,000 in other counties of similar population. In 1952 these same counties had a reported poliomyelitis attack rate of 58 per 100,000 compared with 38 for the other counties. Moreover, in 1952 the counties had an average of 42 paralytic cases per 100,000 population in the 6-9 year age group, which was well above that of the remainder of the country. This factor, plus consideration of the age distribution of the population and the seasonal pattern of poliomyelitis in the area, led to a listing of counties of this size in order of priority for consideration by the state and local health officers concerned, as a basis for selecting the actual trial areas. Many practical administrative matters influenced these officials in making their final selections, including the availability of an adequately organized county health department to carry out the program.

Selection of Study Plans:

1. Observed Control Study. The plan of procedure announced by the National Foundation for Infantile Paralysis and its Advisory Committee was to administer vaccine to children in the second grade of school; the corresponding first and third graders would not be inoculated but would be kept under observation for the occurrence of poliomyelitis in comparison with the inoculated second graders. This has been designated the "Observed Control" study. The plan poses difficulties to objectivity in that knowledge of the vaccination status of a patient is readily determinable and the introduction of even unintentional bias can result; its adequacy would depend upon a high incidence and severity of disease, a high degree of effectiveness of vaccine, and the care with which the data were collected. A number of states, however, had already made their decision to participate on this basis. When finally arranged the procedure was followed in 127 areas of 33 states with total population in the first, second and third grades of 1,080,680. The areas represent complete counties with exception of Kansas City and the town units of Connecticut.

2. Placebo Control Study. Since the problem was to measure the degree of effectiveness, if any, of an untried product, it was important to have data which could provide an accurate gauge of the effect, free of possible bias in diagnosis and reporting. There was introduced, therefore, a second plan corresponding in pattern to that usually employed in scientific investigations. Children of the first, second, and third grades would be combined. One half would receive vaccine; the other matching half, serving as strict controls, would receive a solution of similar appearance which should have no influence on immunity to poliomyelitis. Each child would receive the same lot of material, labeled only by code, for all three inoculations. Only the Evaluation Center would have the key. A single lot of each material was, so far as possible, to be used in a given area. The children in the study would be observed thereafter and all reports relating to a case of poliomyelitis would be made on a concealed or blindfold basis without knowledge of the nature of the inoculum. Although the operative procedures of the placebo plan would require much more work and care, a number of well populated states indicated their preference for it and the "Placebo Control" study was incorporated into the field trial. It comprised 84 areas of 11 states with population in the first, second and third school grades of 749,236. Here again areas represented counties except for the combined areas of New York City and the town units of Massachusetts.

In a short time, plans for collecting and recording information on the involved population were devised by the staffs of the Vaccine Evaluation Center and of the NFIP. A Manual of Procedures provided detailed instructions for the registration, vaccination and follow-up of the children. Great efforts were made to acquaint the responsible administrative groups in the study areas with the need for accuracy, uniformity, completeness in performance and recording. It was clearly emphasized that all areas were part of a coordinated study with the Vaccine Evaluation Center serving as the central agency to which all records would come for assimilation and analysis.

It was readily agreed, as a condition for participation, that local preliminary estimates or reports would not be made until the Center had made a report of the total experience. This was necessary

in order to avoid the possibility of early and unreliable estimates of the effectiveness of the vaccine, based on small numbers and subject to great irregularity.

Identification of the Study Population: It is obviously essential in a study of a phenomenon arising in a limited, selected population that the members of that population be clearly recorded, and their status with respect to the study be established. They constitute the denominator against which all effects are to be measured; hence, any child in the group who subsequently would be reported to have poliomyelitis could be specifically identified. A series of records with cross references was then prepared.

1. Registration. The basic record is a Registration Schedule (Form FT-3) on which was entered the name of each child in a first, second or third grade class of a participating school. Since each sheet and line was numbered uniquely, a person could be permanently identified on that basis. Address, date of birth, sex, color, previous history of poliomyelitis or disability were to be recorded. Furthermore, data with respect to participation and inoculation were subsequently to be entered as a cross check of data on other forms. The same procedure applied to the placebo and observed areas alike. It was necessary in some of the observed areas to emphasize repeatedly that these records were required for the first and third graders who were not inoculated but who constituted the control population. The registration thus obtained constituted the total study population.

2. Participation Request. Each child was to receive a form briefly telling of the pattern of study - observed (FT-1) or placebo (FT-2) - on which a parent could make written request for the child to participate in the study, whether to be inoculated or not. It also gave permission for the collection of specimens of blood, if needed. When a specifically signed request was returned, this fact was to be entered in the proper space on the Registration Schedule. Specific refusals were entered, and when the form was not returned or returned not signed, that was to be appropriately recorded as "no". Certain irregularities were encountered in the observed areas since only one grade was subject to vaccination; for example, request forms were sometimes used only for those control children who were to give samples of blood, so that yeses and noes in those groups could not be fully defined.

3. Vaccination Record. This form (FT-4) was filled out for each person who received an inoculation or from whom blood was taken. It duplicated the identification contained in the Registration Schedule and the name of the signer of the request form. Three injections of 1 cc each were to be given intramuscularly at 0, 1 and 5 weeks, respectively. The date of each inoculation, the lot or code number of the material given, the name of the physician and date blood drawn was recorded. Space was provided for recording any evidence of reactions. When the vaccination series was not completed, the reason was to be stated. The dates of inoculation and of blood specimens were also entered on the Registration Schedule, permitting a check for accuracy or inconsistencies.

Table 1a. Distribution of Study Population by Participation Status and Vaccination Status - Placebo Areas

Study Population	Number	Percent
Total in Grades 1, 2 and 3	749,236	100.0
Total requests to participate	455,474	60.8
Complete series of injections:		
Vaccine	200,745	26.8
Placebo	201,229	26.9
Incomplete injections:		
Vaccine	8,484	1.1
Placebo	8,577	1.1
Absent at first clinic or withdrew	36,439	4.9
Number not requesting participation	280,868	37.5
Participation status not recorded	12,894	1.7

After a careful check of the registration records with enrollment figures for the first three grades in each participating school, submitted to the Center at the time of the vaccination clinics, and persistent effort on the part of the Center staff through correspondence and personal visits to more than 30 trial areas during the course of the summer and fall, complete registration was obtained from all schools in the placebo areas except for six schools where the children whose parents refused participation were not included. In the observed areas complete records were obtained from all except twenty-six schools with a total estimated enrollment in the first three grades of 916 or .08 percent of the total observed area study population.

These essential records were prepared in triplicate. When vaccinations were completed and the blood specimens collected, they were to be edited locally and the first two copies sent to the State Health Department which, after review, would send the original copy of the Registration Schedule and the Vaccination Record to the Evaluation Center. The extensive work involved in editing, completing and processing these records is detailed in appendix.

4. Procurement of Blood Specimens. The only data with respect to the antibody response of humans to vaccine of the nature employed in the field trial were those reported by Dr. Salk. But there was only a small number of laboratories in position to undertake studies on the scale projected and few with experience in extensive serologic testing. In order to gain information of the responses to different lots of material subjected to transportation and variable field field conditions, it was decided in consultation with experts in the laboratory investigation of poliomyelitis to obtain specimens of blood prior to inoculation from a two percent sample of children who were to receive vaccine, and from controls, and from these same persons again two weeks after vaccinations were completed. By titration of the sera for antibody levels by means of tissue cultures of monkey kidney or HeLa cells, evidence would be provided regarding the occurrence of antibodies to the different types of poliomyelitis virus in the various parts of the country and the changes in titer induced by vaccine. It would give a view of the variation in the potency of lots of vaccine or of the same lot in different areas. Moreover, the results could be measured in persons without demonstrated antibody to any type in comparison with a reinforcing effect in persons who already possessed some antibody. The specimens from control subjects would also provide a base line for measuring any concurrent changes which might take place in the population through natural exposures, and permit accurate conclusions as to the antigenic activity of the vaccine. It was also urged that blood specimens be obtained from the same persons again at the end of the poliomyelitis season of 1954; this was carried out in November. The laboratories would be uninformed as to whether the specimens were from a vaccinated or control child and the tests would largely be done on an unselected basis.

Number of Blood Specimens Collected at Pre- and Post-Vaccination Bleedings and Third Bleedings in November

	First Bleedings		Second Bleedings		Third Bleedings
	No.	%	No.	%	No.
Placebo areas	14,475	100.0	12,382	100.0	11,870
Vaccinated	7,220	49.9	6,210	50.1	1/
Placebo	7,255	50.1	6,172	49.9	1/
Observed areas	26,406	100.0	20,046	100.0	20,931
Vaccinated	9,789	37.1	7,870	39.2	1/
Controls	16,617	62.9	12,176	60.8	1/

1/Data by vaccinated and control population not yet available.

With the assistance of Doctors Kumm and Boyd of the NFIP, additional laboratories were enlisted and additional funds provided, if needed, so that 28 laboratories geographically distributed finally joined in the study. Arrangements were made with the Connaught Laboratories to prepare standard lots of Types I, II, and III viruses individually which could be distributed to the laboratories for the test. Standard type specific monkey sera for controls would be distributed by Dr. Herbert Wenner. At a second meeting of the participating investigators, the metabolic inhibition test with monkey kidney cells of Drs. Salk and Youngner was demonstrated. It was agreed that this or HeLa cell technic would be used and provision was made for those not familiar with the technics to visit the appropriate laboratories. A supply of cultures of HeLa cells which could be shipped to the requesting laboratory was arranged by Dr. Kumm with the Tuskegee Institute Laboratory.

It was decided to use a series of single culture tubes and original serum dilutions of 1:4, 1:8, 1:16, 1:64, 1:256, and 1:1024 with 100 tissue culture doses of virus for testing of the sera. Standard forms (FT-11) for reporting results were drawn up. Subsequently, other modifications in culture technic were added. It was necessary to allocate the areas to the respective laboratories and to establish working relations with the responsible local authorities in the study areas.

Dr. Herbert Wenner joined the Evaluation Center staff temporarily and visited all the laboratories concerned. He drew up a Manual of Laboratory Procedures which was to be followed. Arrangements were made for exchange of sera between laboratories for cross reference and standardization and a high degree of cooperation developed. Delays inevitably occurred owing to need for experience with technics and with equipping and staffing laboratories for this large scale of work.

5. Reactions. Because of the natural concern with reactions which might occur with a new product in large scale use, the Manual of Procedures emphasized the need to record any untoward reactions which appeared to be related or coincidental to the administration of vaccine. A further notice from the Evaluation Center asked for notification by phone of any circumstance of significant severity which might be related to the inoculations.

During the course of the vaccination of children in Pittsburgh by Dr. Salk, a concurrent study was carried out in March and April of 1954 by the Evaluation Center concerning cause of absenteeism in vaccinated children as compared with their classmates who had not received vaccine. The bulk of these data had been collected by Dr. Salk before the Center entered the study. They were analyzed and, in addition, a system was developed for recording absences from school and verifying the cause of ab-

senteeism through the school health service. Significant illnesses were investigated further through personal consultation with the attending physician and the family. Initially the experience in 20 public schools during each of five weeks following vaccination was recorded for 3,246 vaccinated children and 1,773 non-vaccinated children. Total absences during this period were 2,270 for the vaccinated and 1,611 for the non-vaccinated. When absenteeism is analyzed by interval after the vaccination, the only apparent difference between the two groups exists in the first week. Absenteeism is somewhat higher in the non-vaccinated group, 31.5 percent compared to 22.9 percent. It seems likely that this is due to the fact that children who were absent were by that fact alone not included in the vaccinated population at the time of clinic.

Information on reason for absence was tabulated in similar fashion for each of the five weeks following vaccination for those receiving vaccine and those not receiving vaccine. Here again, according to the 29 itemized causes, no significant difference was observed between the two groups. Only one case of nephritis occurred and that in a non-vaccinated child during the first week after first clinic.

It seemed advisable to extend these studies further to an additional group of schools for more thorough follow-up as to extent and cause of absence. The procedure was identical with that described above, although greater effort was put into obtaining accurate medical information on the causes of absenteeism. In the five schools studied, there were 969 vaccinated children and 486 non-vaccinated; of the latter, 380 had not requested vaccination and 106 had requested but were absent on the day of the first clinic. Study of the total absenteeism by week and by days within weeks during the 3-week period after the clinic merely served to confirm the earlier observation that absenteeism was identical in the two groups. The only difference, again, was observed in the first week when absences occurred among 16.1 percent of the vaccinated compared with 41.6 percent among the non-vaccinated. This was accounted for largely by children who had requested participation but were absent on the clinic day. Again, detailed examination of the reasons for absence failed to reveal any significant differences between these two groups during any of the weeks of study. The one case of kidney disease which came to attention occurred in a non-vaccinated child. The great bulk of remaining causes of absence might be defined as respiratory in nature and did not differ in the two groups. The findings from these two studies were made available to those concerned with final decision as to whether the field trials were to be conducted as planned, and served as additional assurance at that time of the safety of the product.

A further study of reactions established by members of the staff in conjunction with health authorities of Schenectady, New York, where vaccine and placebo were used, will be reviewed later in this report.

Vaccinating Procedure and Assignment of Controls

Placebo Areas: The materials to be used in placebo areas were supplied in boxes containing six vials of 10 cc content; three of them contained vaccine and three contained placebo, each set of three labeled with a code number unique to that set. A vial was entered with a new, sterilized needle attached to a freshly sterilized 5.0 cc syringe. That volume of fluid was withdrawn and the needle left in place. Then with a new needle for each injection, 1.0 cc of the material was given to each of five children in the left triceps muscle. A new syringe was then used

Table 1b. Distribution of Study Population by Participation Status and Vaccination Status - Observed Areas

Study Population	Number	Percent of Second Grade	Percent of Total Population
All Grades - Total	1,080,680		100.0
Requests	567,210		52.5
Second Grade - Requests	245,895	69.2	22.8
Complete vaccinations	221,998	62.4	20.5
Incomplete vaccinations	9,904	2.8	0.9
Absent or withdrew	13,993	3.9	1.3
First and Third Grades - Requests	321,315		29.7
All Grades - Participation not requested	332,870		30.8
Participation not recorded	180,600		16.7

to remove the remaining 5.0 cc from the vial which was given as before to five additional children. (In a few areas, separate syringes and needles were used for each child.) The exact code number of the material given was recorded. Following the same procedure, the next ten children received the material from a vial bearing the second code number, indicating that it was different from the first. The remaining four vials were then returned to storage until the next clinic when the same children would again receive their inoculations from the specific vials with the same code numbers as before. This required careful attention to procedure and to identification of each child. Provision had to be made for consultation with the Evaluation Center for replacements or additions when shortages developed, without revealing the code or the nature of material in question.

The classroom groups of the first, second, and third grades constituted the basic clinic unit and remained so through the three inoculations. Consequently those receiving vaccine or the corresponding placebo were segments of the same group and the controls were clearly designated. In general, only one lot of vaccine or placebo was used in a placebo study area or in a school. Because of supply problems this was not completely uniform, and in 14 placebo areas more than one lot was employed. Even then, the uniformity in the 206 schools of those areas was maintained and the controls for each lot of vaccine were clearly designated on the 22,997 records according to corresponding codes.

In 346 schools, with small classes, the numbers were insufficient to complete the use of a 10 cc vial - the required procedure; thus, 1529 children received only placebo. This was balanced by 1761 children in 387 other small schools who received only vaccine. But it is important to emphasize that the equal distribution of vaccine and placebo held at every level. Moreover, according to our records, out of a total of 1,237,446 injections in 419,035 persons inoculated in placebo areas, only 748 persons received a mixed series of vaccine and placebo.

Observed Areas: In observed study areas where only those second grade children whose parents requested participation were vaccinated, the problem of establishing the control population was more complex. After careful consideration of various alternatives, it was decided that the total first and third grade study population compared to the vaccinated second grade population would be the most critical measure that could be applied to measure the efficacy of the vaccine. This was also the original premise on which various state health offices agreed to participate in the study. In observed areas there was a greater number of instances in which more than one lot of vaccine was used in an area, which came about partly as a supply problem and partly from a decision to use, for the third inoculation, lots which appeared upon test to be stronger antigenically in combination with those which appeared to be only moderately so. This resulted in as many as seven or eight different lot combinations being used in some areas. Naturally, it resulted in further irregular lot combinations being used in a single school. There were 268 schools out of 7925 in observed areas where this occurred, involving a study population of 51,157 of whom 11,533 were vaccinated, or five percent of the total complete vaccinations in observed areas. Since it was impossible to determine the proper controls for each lot combination in these schools, they have been given a separate designation in the report as "mixed lots within schools" for both the vaccinated and control populations.

In 765 other observed area schools there were a few children who received a lot combination different from the major series used in the school. In these schools involving a vaccinated group of 39,914 children where only one, two, or three second graders received a series of lots different from the rest of the vaccinated group, the total first and third grade populations were taken as the control populations for the major lot combinations and specific controls for the 1,144 children receiving odd combinations were not established.

Staff Supervision: During the vaccination period, April 26 to June 15, members of the Evaluation Center staff visited 32 of the 44 participating states to inspect or correct procedure and to ensure proper recording and understanding. It was necessary to prepare additional memoranda specifically restating the requisite information and the need for uniformity and completeness of the data to be supplied in the records. The problems of vaccine replacement and the completing of inoculations in migrant children were also handled. In the field more than 150,000 persons assisted in the total program, including clinicians, epidemiologists, health officers, physical therapists, public health nurses, virologists, school teachers and administrators, and local volunteer recorders and clerks.

Instructions for the reporting and investigation of cases of poliomyelitis occurring in the study population were reinforced with specific memoranda and forms for use in this phase of the field trial were drawn up and distributed to the trial areas.

Identification and Verification of Reported Cases in the Study Population

The second phase of the study was that of determining the occurrence of poliomyelitis among members of the study population, of identifying the patient, and of establishing diagnosis by integration of clinical, epidemiologic and laboratory data which could contribute reliable, objective information. It was apparent that with the large number of different professional personnel involved in the widespread study, variability could be expected. By seeking uniformity of understanding and performance it was

hoped that the variations could be reduced, and that 211 different patterns could be avoided even though the Evaluation Center was completely dependent upon the ability, willingness, and collaboration displayed at the local level where the cases of poliomyelitis would occur.

To reduce the need for discrimination locally, to encourage completeness of reporting and uniformity of procedure, a single plan was instituted for the investigation of all cases in the entire study population; that is, cases arising in any member of the first, second and third grades during the spring of 1954, whether inoculated or not, whether participation had been requested or not. Every case, paralytic, non-paralytic, suspect or doubtful was to be reported to the Center and subjected to the same degree of study, recognizing at the same time diagnostic problems of the early acute phase and variation in medical interpretation. All cases in families containing a member of the study population were also to be reported but subjected to limited investigation except as special studies.

Reporting of Cases: Because there may reasonably be delay between the onset of a case of poliomyelitis and its diagnosis as poliomyelitis, it was urged that the local agencies try to reduce any further delay in reporting of a case to the health department or program director.

As a means of following the occurrence of poliomyelitis in each of the trial areas as closely as possible, both in the study population and in the family associates of study members, a weekly reporting system was established as of May 1, 1954, whereby all reported cases of poliomyelitis in each trial area were submitted to the Vaccine Evaluation Center weekly on Form VEC-11 which called for the name, age, date of onset as given, city of residence, grade if enrolled in school, and type of case. Each area was also asked to report all deaths from all causes in the study population on these weekly reports. This plan proved to be too slow and local health officers were subsequently requested to notify the Evaluation Center by collect telegram immediately upon notification of a case. It was then possible promptly to send back to the Health Department schedules listing the further information to be obtained and the date on which each item was due.

In addition to this reporting system, arrangements were made with the National Foundation for Infantile Paralysis to obtain photostat copies of all NFIP medical care, hospital admission and discharge records for children in the age group five through nine in each of the trial areas. These records were cross-checked with the VEC-11 reports submitted by the local health officers as a means of spotting any eligible cases which had not been reported. In each instance, if notification to the Center of the usual reportable clinical case was not forwarded by the local health office, correspondence was initiated by the Center to determine if the case was in the study population.

The total of cases reported from each trial area each week was compared with the standard reports issued by the United States Public Health Service as a means of determining if adequate coverage was being obtained from the trial areas. The need to find cases in study members who migrated to other trial areas or communities outside the trial areas was strongly emphasized, and many cases which would otherwise have been lost to the study were thus recovered.

Through these methods assurance was gained that the Center was informed of a high percentage of all cases in the study population considered to have poliomyelitis even though delays in notification and investigation inevitably occurred. Not more than a half dozen cases were disclosed to have escaped the established procedures for identification and these were essentially migrant children.

Investigation of Case: Upon report of a case of poliomyelitis, the health department needed to arrange promptly for the successive steps in investigation. Since a high percentage of patients was admitted to the hospitals (88.9 percent in placebo, 85.9 percent in observed areas) not always in the same county, various means of carrying out the requirements were devised. The responsibility, however, remained with the local director of the study. In a number of instances the state or district authorities assumed all responsibility. Great assistance was provided in a number of areas by the Epidemiologic Intelligence officers of the USPHS assigned through Dr. Alexander Langmuir to state health departments and laboratories participating in the study.

1. Clinical-Epidemiological Report. As soon after onset - or report - as possible, a summary of the clinical history and examination, including spinal fluid, of the case was to be made on the proper form (FT-6) together with the diagnosis at that time. On the same form the family history with respect to concurrent illness or previous poliomyelitis was to be recorded. Administration of gamma globulin to family members was also to be recorded. This information constituted the first official record received at the Evaluation Center and contained the tentative diagnosis. It provided also a basis on which to proceed with subsequent studies or to eliminate the patient from consideration if obviously his illness was due to another cause. Much of this was done by staff physicians but public health nurses also contributed a large part. No case was accepted as part of the study unless this record was received; thus, for every case disclosed by any means an FT-6 record was obtained.

2. Laboratory Specimens. As early as possible a specimen of stool (or two) and a specimen of blood

were to be collected from the patient and sent promptly to the laboratory functioning for that area. They were accompanied by forms (FT-9) identifying the patient and the dates of collection. Copies of the forms were to be sent to the Center - if not received, it was assumed the specimens had not been collected and the health officer was notified of the deficiency.

After three to four weeks a second specimen of blood was to be obtained and, together with the first sample, antibody titrations for diagnosis of poliomyelitis were made. The stool was to be studied for the presence of poliomyelitis or other virus. In some areas studies of familial associates were also carried out by the laboratory and the local health authorities.

The complete laboratory report was made directly to the Center on Form FT-10, although preliminary reports were sometimes made by letter.

At first, the same serological procedure was employed for the testing of sera of patients in the study areas as was used for study of pre- and post-vaccination sera. Later it was agreed that it should be more sensitive and titrations were made with 2-fold dilutions and four tubes per dilution to reach the end-point. In some instances this was preceded by a preliminary screening. In addition, Dr. Wenner and Dr. Frisch provided to all laboratories supplies of standard human sera with titers in the range ordinarily encountered in man. Additional spot checks for variability in laboratory results were made at different times by a single pair of sera sent to all laboratories.

Virus isolations, from stool specimens primarily, were attempted in monkey kidney cells or HeLa cells and generally a negative specimen was retested at least once. The information gradually accumulated to indicate that HeLa cells might be less sensitive and again exchange of specimens among a series of laboratories was made to test this probability - which proved to be correct. Subsequently, when HeLa cells were used, passages were to be made three times before considering the test negative. In some instances specimens were also tested by the inoculation of monkeys. In a number of instances serologic tests were carried out against mumps, choriomeningitis and encephalitis viruses as well.

In addition, the laboratories frequently played a large part in collection of specimens, of maintaining the attention of health and hospital personnel in the continued need for proper specimens and prompt delivery. There is little doubt that the present experience will have done much toward prompt laboratory diagnosis of poliomyelitis.

3. Examination by Physical Therapist. On the recommendation of clinical consultants it was decided that an expert examination of the patient's muscular status should be made 10 to 20 days after onset of illness. At that time the febrile stage of the disease is commonly past and further progression of paralysis is unlikely. Furthermore, spasm and tenderness are generally diminished and a reasonable measure of disability can be obtained. Again, in an effort to gain uniformity, the physical therapists who agreed to participate had received or did receive a two weeks' course of orientation in an abridged system of muscle examination and in grading of muscles or muscle groups according to a uniform system of recording disability which gave a score of involvement based on muscle mass and severity of dysfunction. This system had been devised by Dr. Jessie Wright and the instruction was given under the supervision of Miss Miriam Jacobs at the D. T. Watson Home in Pittsburgh, Pennsylvania. It had been used by many of the same physical therapists in the field study of gamma globulin carried out by the Communicable Disease Center, USPHS, in 1953. The study areas were apportioned among 67 physical therapists by Miss Lucy Blair of the American Physical Therapist Association, who enlisted their aid.

Accordingly, at the time the other procedures for study of a patient were instituted, the local health officer was to notify the designated therapist of the identity and location of the patient with a request that the examination be made at the proper time. The examiner was not informed of the patient's vaccination status and was to conduct the examination on all cases reported to be poliomyelitis whether considered to be paralytic or not. At that time it was requested that provision be made for a review and interpretation of the case by a physician especially skilled in the clinical aspects of poliomyelitis. This was to be recorded on the same form and became the established clinical diagnosis. Provision for securing this specialist's report was again left to local authorities and done under a variety of arrangements, often through the local medical society. In many of the hospitals to which the patients were admitted the specialist was readily obtained. When completed, the examination record (FT-7) was to be returned to the local health department and forwarded to the Evaluation Center.

It was further agreed that the examination should be repeated 50 to 70 days after onset. By this time the patient may have experienced the major proportion of muscular recovery but, on the other hand, defects not clearly localized earlier may have become more apparent as activity or use of the muscles increased. The other interferences of the acute stage will be absent so that residual injury can be more accurately measured. The specialist's interpretation of the entire character and course of the case would be expected at this time as well. This form (FT-8) transmitted to the Center by way of the State Health Department, was the last of the field investigations which provided the basis for clinical classification of the patient.

The cross-responsibilities and communication

difficulties often resulted in delays in receipt of the reports, even when completed expeditiously by the physical therapist. The consultant's diagnosis and comments were often difficult to obtain and the records of muscle evaluation not infrequently were simply not forwarded promptly.

4. Fatal Cases. It was requested that any fatality in the study population be reported by telephone to the Evaluation Center and that every effort be made to obtain a complete autopsy, central nervous system tissue and other specimens for laboratory study. Early in May, a special message was sent to all study areas asking that any fatal cases in inoculated children up to four weeks after last injection be given special attention. The Evaluation Center and the regional laboratory were to be notified immediately, and a complete post-mortem examination should be sought and made by a well qualified pathologist with specimens provided to the laboratory. Clinical and epidemiological reviews were to be made. The Center offered to assist in obtaining the desired personnel if necessary and to meet expenses incurred in fulfilling the requirements.

5. Steps to Maintain Completeness of Investigation. The substantial amount of correspondence required very early in the trials concerning proper field follow-up and collection of specimens pointed up the fact that clarification of the needs was necessary beyond the printed instructions. Meetings were held in May and June in study areas with state and local health officials, state and local NFIP representatives, and interested hospital personnel in 32 of the 44 states in the trials. At these meetings staff members of the Evaluation Center reviewed the requirements for follow-up and the local plans for this phase of the operation.

By July the pattern of the deficiencies in case studies had become quite apparent, and steps were taken to correct them. Physician's interpretation and signature as required on the FT-7 and FT-8 forms were frequently missing. Therefore, a form letter was developed which provided a convenient means for promptly requesting the missing information. Each participating laboratory was sent a list of all cases on record in their area and all reported specimen collections. Thereafter, a postcard reporting this information to the laboratory on all newly reported cases became standard operating procedure so that the laboratories would have a complete record of cases from whom specimens should be anticipated.

A system of logging each case by area was also put into effect at the Center. The log served several purposes. It provided a complete and compact record wherein receipt of the various forms required by the follow-up could be posted. At intervals during the latter part of the year a summary of the incomplete records in the log was mailed to each state health officer for any cases in his areas.

In an effort to point up the importance of getting qualified review and interpretation of reported cases on the FT-7 and FT-8 forms a general letter was mailed to all state health officers on August 27, re-emphasizing the need for a specialist's comments and interpretation on the back of the physical therapists' forms and asking that the professional status of the physician be indicated below his signature. In this letter the states were again reminded to furnish the Center the names and qualifications of the specialists they had selected for this purpose if they had not already done so.

Late in September it became evident that on receipt of case records attention to all phases of the investigation should be re-emphasized to the field and that the waiting period for each of the forms should be reduced. A form (VEC-31) was developed for this purpose as a Special Attention note sent on each case, showing the dates on which each report was due in the office of the Evaluation Center. The request for specialist's comments, signature and status was stressed by a quote from the VEC letter on this subject clipped to the VEC-31 forms.

After the middle of November lists again were prepared showing missing data and sent to state health officers requesting immediate action. Telephone calls were made to a number of the areas.

As of December 31, a tally of the incomplete study cases showed that there were approximately 290 incomplete study cases out of a total of 1103 reported. An intensive follow-up by telegram, telephone, letter, and field visit was made during January, and the open cases were reduced to 78 as of January 31. The last of the delinquent reports was not received until March 9, 1955.

Formulation of Criteria for Diagnostic Interpretation

It became apparent early in the examination of case records that a substantial body of data would need to be reviewed before generalizations and limits of variation could be established. Moreover, this must be done by repeated examination of the accumulating data without respect to the vaccination status of the patient. The policy was adopted that effort should be made to establish criteria on the basis of objective analysis, to formulate them clearly, and to apply them to each case before any attempt was made to divide cases into vaccinated or control groups. Consequently, attention and effort was concentrated on obtaining complete and reliable data. The data from each report were reduced to punched cards from which in turn mass listings and tabulations could be made for study. Since there was a minimal interval of three months between the onset of a case and receipt of the final report, the complete data accumulated slowly. Nevertheless, as significant amounts became available the compiled data

were subjected to careful study. Once again, it is important to emphasize that this was not an evaluation of data from a single investigative unit, but from many sources; and while the procedures employed were basically standardized, qualitative and quantitative variation was quite evident. Interpretation must, of necessity, accept that fact.

Definition of Paralytic Status and Severity: The physical therapist's examination was recorded on two forms (FT-7 and FT-8) which listed muscles or muscle groups on the basis of their anatomical mass, rather than by functional importance. The examiner was to enter a standardized estimate of the degree of impairment for each unit, grading from normal through five increasing degrees of severity: good, fair, poor, trace, or no power. Involvement of muscles supplied by cranial nerves and of the muscles of respiration was recorded with limited score without grade of severity. It became evident that special problems existed: the neck and abdominal muscles are obviously affected by muscular spasm and pain; asthenia of illness made the significance of minor muscular weakness difficult to determine. It was necessary, then, to adopt criteria uninfluenced by other data, defining what extent of involvement would be required in order to consider a patient to be "paralytic" and, conversely, what would categorize the patient as "not paralytic". In reaching the conclusions, Doctors Bennett, Green, Hodes, Top and Wright gave continuously of their time and expert judgment. They intensively reviewed tabulated data of muscle examinations, both early and late, unexposed and hence uninfluenced by other clinical details, the laboratory findings or the vaccination status of the cases.

A. Minimal criteria for classification of a reported case as paralytic were then adopted.

1) The following would be excluded:

a) Abdominal and neck muscles graded, bilaterally, good or fair.

b) Other muscles graded bilaterally good.

c) Record of hoarse voice without supporting evidence or comment. A check mark indicating deviation of the palate without supporting evidence or comment.

d) All ratings of good would be eliminated from scoring.

2) The following would be accepted as significant:

a) Spotty asymmetrical involvement with a grading of good recorded on either first or second muscle examination, in muscles characteristically affected by poliomyelitis: deltoid, triceps, finger extensors, opponens pollicis, gluteus medius, quadriceps, gastrocnemius, anterior tibialis. They would comprise Grade I of paralytic (spinal) without score.

b) A grade of fair of a single muscle or single muscle group. It would receive the appropriate score.

c) Definite indication of facial, laryngeal, pharyngeal involvement alone, or of palate with supporting evidence. It was decided to consider bulbar involvement independent of score.

Any of these involvements may have completely disappeared by time of the second examination or may be first recognized at time of the second examination. The physician's diagnosis and comments were of major value in these reviews.

The elimination of all good muscles from scoring, as well as muscles innervated by cranial nerves, and respiratory muscles would provide for a maximal score of 440. However, all tabulations have been arranged so that any scoring system can be employed for further analysis.

B. Further examination of the data resulted in the following classification of spinal paralytic involvement on what appeared to be group characteristics. Grade I might be termed "minimal paralytic without a score", and frequently such cases were questionable clinically. Grade II might be termed "minimal with a score".

Grade	Score
I	0
II	1-19
III	20-89
IV	90-199
V	200+

C. An effort was also made to assign grades of severity to bulbar involvement apart from those specifically excluded.

Grade 1 - listing of involvement by physical therapist without comment, minimal or doubtful.

Grade 2 - one area of involvement with supporting comment or two areas commonly related - definite.

Grade 3 - distinct difficulty swallowing including previous grades in combination. Other moderate involvement.

Grade 4 - required tracheotomy in addition - or at times respirator.

Involvement of diaphragm and intercostals with or without use of respirator was considered independently.

Cases with spinal and bulbar involvement could be classified into grades of spinal involvement with the accompanying bulbar severity designated.

This, then, was adopted as the basis of classification according to paralytic status with which the data from other clinical reports and laboratory data would be integrated to furnish a final diagnosis. In 37 instances (9 percent) in the placebo areas the 10 to 20 day examination of the musculature was not done, and in 11 (3 percent) the second was not obtained; in the observed areas 81 (14 percent) first examinations and 19 (3 percent) of the second were not done.

Interpretation of Laboratory Investigations

Since the laboratories engaged in the diagnostic studies were also busily engaged in the testing of pre- and post-vaccination sera, and since a number of them had to develop facilities for the work, certain delays in obtaining the results of their studies were anticipated. By the end of October a limited number of complete reports had been received. The examination of stool specimens for virus had proceeded ahead of the serologic studies which of necessity awaited the receipt of a sample of convalescent blood. At the time the books had finally to be closed to new entries, the number of reports had mounted progressively so that the following record existed for cases occurring after mid-June 1954.

Status of Laboratory Data on All Cases in Study Population

Areas	Cases	Stool-not done or not collected		Serology-not done or not collected		No lab reports	
		No.	%	No.	%	No.	%
Placebo	428	56	13.1	80	18.7	14	3.3
Observed	585	101	17.3	92	15.7	44	7.5

It must be recognized that omissions represent specimens which were unsatisfactory, others not received, as well as those which were not collected so that the uncompleted laboratory examinations represented a small number.

The results of tests for virus isolations were classified as positive, negative, no specimen or unsatisfactory, virus other than poliomyelitis, poliomyelitis virus of type unidentified, or test not done. From 72 patients viruses were recovered which have not been identified as poliomyelitis. Whether they are primary or coincidental infections is not completely determinable at this time.

Interpretation of serological studies was more complex. The reported results of neutralization tests done in tissue culture were subjected to analysis. The levels of titers obtained varied moderately among the laboratories.

From 426 patients, a typed poliomyelitis virus was recovered and in 376 of the instances serological tests were also done.

Reported Isolations	Total		Virus Type I		Virus Type II		Virus Type III	
	No.	%	No.	%	No.	%	No.	%
No. with virus recovered	426	100.0	238	55.9	53	12.4	135	31.7
No. with serologic test	376	88.3						

299 tests (79.5%) with paired sera - first obtained 14 days or less after onset.

67 tests (17.8%) with single or paired sera - first obtained 15 days or later after onset.

10 tests (2.7%) with single serum - obtained 14 days or less after onset.

Of the 299 tests in which the first serum was collected less than 15 days after onset, only 44 percent revealed a 4-fold or greater rise in antibody to the homologous virus, but in 67 percent of these tests antibody to only the homologous virus was present in the patient's serum. In the other 67 tests the first serum or the only serum was obtained 15 days or more after the onset; they are considered to represent only the convalescent phase serologically. But when they were added to the previous group the percentage of total with antibody to only specific type of virus isolated from the patient was still 67 percent. It is reasonable to conclude that the solitary antibody had resulted from the current virus infection, particularly since it specifically agreed with the type of virus recovered. It indicates, furthermore, prior to this illness those persons had no antibody to any of the three types of poliomyelitis virus. On the basis of these observations, while a rise in titer was considered a definite positive, a substantial level of antibody to the homologous virus only in first and second specimens, or in a late serum alone, without rise in titer was considered probably positive.

It is of interest, moreover, that in these data there is no indication that infection with one type of virus induces antibody to heterologous types in persons without previous experience, at least under the conditions of measurement employed.

Table A. Serologic Rises in Cases with Virus Isolation*

Collection of first blood - days after onset	Total	4x rise homologous type only	No rise or irregular changes	4x rise to more than one type	% 4x rise homologous type only
Total	356	145	191	20	40.7
0-4	76	33	38	5	43.4
5-9	147	71	65	11	48.3
10-14	76	28	45	3	36.8
15-29	44	11	33	0	25.0
30 or more	13	2	10	1	15.4

*Includes only cases with 2 specimens of serum

When the first serum was obtained before the tenth day, a 4-fold or greater rise was demonstrated in 47 percent of the second sera; thereafter, the frequency diminished progressively.

It is also clear that if the initial titer were 32 or less, in 78 percent of the second sera a 4-fold or greater increase was noted while in only one-third of those with initial titers of 128 or more was this rise observed. Hence, the presence of titer of 32 or more to the homologous, even with low titers to other types, was considered suggestive. In the absence of virus isolation the probable and suggestive interpretation may be less secure because an illness resembling poliomyelitis might occur in a patient who had earlier acquired antibody against a single type of virus, but it can be accepted that if the acute illness now observed was poliomyelitis the type of virus is, by these criteria, serologically indicated.

Table B. Serologic Rises in Cases with Virus Isolation According to Level of First Serum Specimen*

Level of first serum	Total	4x rise - homologous type only	No rise	% 4x rise
16 or less	46	40	6	87.0
32 or less	80	62	18	77.5
64 or less	108	79	29	73.1
128 or more	150	51	99	34.0

*Excludes 18 cases with unsatisfactory serological tests, 6 cases with no antibody in acute or convalescent serum, 20 cases with 4-fold rise to more than one type and 54 cases with first blood collected after 14 days.

The following criteria for interpretation of serologic results were drawn up:

A. With Poliomyelitis Virus Isolated:

1) Positive - 4-fold or greater rise to homologous type only.

2) Probably positive - antibody present at level of 16 or more in first and second sera to homologous type only without rise; in convalescent serum 15 days or later when earlier specimen was not obtained.

3) Suggestive:

a) Level of 32 or more to homologous type; present at low levels to heterologous type.

b) 2-fold rise to homologous type only.

4) Indeterminate:

a) only acute stage serum available - less than 10 days.

b) multiple antibodies - no distinctive change, or irregular changes up or down.

c) 4-fold rise to more than one type.

5) Negative:

a) no antibody to any type in first and second sera or in second serum alone.

b) low levels, 4 to 8, to one or more types - no rise.

6) Inconsistent - did not agree with type of virus reported.

7) Reports of serologic evidence of other etiology.

B. No Isolation of Poliomyelitis Virus or No Test for Virus:

1) Positive - 4-fold or greater rise to one type of virus only.

2) Possibly positive or suggestive - the criteria called probably positive under A above, when limited to one type only with or without 2-fold rise. Also - high level to one type only with or without 2-fold rise and low levels to other types.

3-7) As above

C. When other virus alone is reported, criteria B were followed. It is not certain at present to what extent those reports represent other viruses alone, or mixtures. The latter have been demonstrated in some instances. In addition, typings have sometimes been obtained only after monkey passage.

D. In some laboratories studies of the family associates have been conducted. When virus was isolated from the family and not from the patient, criteria A were employed.

Integration of Data for Final Diagnosis: Although the frequency with which virus was isolated tended to increase with increasing clinical severity of illness, the failure to recover virus from a significant number of characteristic paralytic cases indicates that lack of virus isolation is not sufficient at this time to eliminate the patient from classification as poliomyelitis. Consequently, a combination of clinical findings, muscle evaluation, and laboratory data have been utilized in arriving at the final classification - but it should be re-emphasized that this was done without information of the vaccination status of the patient. The criteria for classifying illness other than paralytic polio (see page 9) were then formulated.

A. Not Poliomyelitis: Those cases where the clinical record and comments or later communication indicated other disease.

Cases with lack of common symptoms or signs of poliomyelitis and examination of spinal fluid negative or not done.

Cases in which orphan viruses, or Coxsackie virus only were isolated, or serological evidence of active infection with mumps virus.

Cases with no antibody to poliomyelitis virus detected.

B. Non-paralytic Poliomyelitis: It is recognized that this is a difficult group to define, shading gradually into cases in the minimal paralytic class. They were cases called poliomyelitis by the physician, exhibiting characteristic clinical features, with positive spinal fluid, with or without virus isolation or positive serology but without presenting significant evidence of muscular impairment.

C. Doubtful Poliomyelitis: There remains a group which on careful review of all data leaves a decision in doubt as to whether they are poliomyelitis.

D. Fatal Cases: In these instances great effort was made to obtain an adequate record of the patient's history and course, to urge post-mortem examination and to obtain a complete report. When possible histological sections were obtained for review by consultants. In some instances the examination was conducted after embalming and specimens for laboratory study were only then obtained. In others, the post-mortem was done without obtaining laboratory specimens; in others, no autopsy was done.

Diagnosis of poliomyelitis was based upon history of characteristic severe disease, histologic evidence described by a well qualified pathologist, with or without isolation of virus.

Cases were considered not to be poliomyelitis on the basis of history indicating specifically other disease; major pathologic evidence at post-mortem of other disease, and lack of characteristic changes in the bulb or spinal cord. No poliomyelitis virus was recovered from these cases.

Controls in Observed Control Areas: The data from many investigations have indicated that infection with poliomyelitis virus occurs at an earlier age in lower socio-economic groups than in the higher. Certain factors related to these characteristics might be involved in the decision as to whether parents requested participation of their children in the vaccination program and thus affect the composition of the groups. Therefore, differences in susceptibility related to these variations among the participants and non-participants might be encountered in the study population. Accordingly, at the request of the Evaluation Center, the Survey Research Center, University of Michigan, in December 1954, conducted a survey of the educational level, health consciousness, living conditions and community activities of a portion of the study population in 10 of the 11 placebo control states. A sample of 1300 families of study members was carefully selected so as truly to represent the total study population of these areas. Eleven hundred two families were interviewed; 665 being participants, 56 who requested participation initially but failed to attend clinic, and 381 who did not request participation.

Interviews were conducted by trained interviewers who had no specific knowledge as to the underlying purpose of the study and hence were not biased in their questioning, nor were the respondents aware that the questioning was related to poliomyelitis or the field trial in any way.

Among other things the schedule of questions dealt with the following items of information: size of family, frequency of illness, use of medical services, parental appraisal of child's health, attitude toward prophylactic inoculations and extent of their use in the study child, knowledge about poliomyelitis, physical facilities of the home, parents' extra-household or community activities, parental occupation and educational level, age of mother, annual income, and an assessment of living conditions and of the type of neighborhood. There is much of interest in the details of this survey report; however, for the purpose here, it is sufficient to summarize by itemizing those factors which seemed to be positively correlated with participation in the field trial. The following differences in the participating groups compared with non-participants were significant at the 99 percent level of confidence.

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

2. Participants more frequently stated that "shots always work" than non-participants.

3. Mothers of participants were more likely to spend two or more evenings a week in outside activities than were mothers of non-participants.

4. Mothers of participants were more likely to have completed high school than mothers of non-participants.

5. A much smaller percentage of participants had family incomes under $4500. Participation rate increased steadily with increasing income.

6. Finally, 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.

Another refinement in the analysis dealt with the extent of participation according to the same characteristics but subclassified as to whether the child was a member of a high, medium or low participation school. These findings have interest in connection with the question of motivation but add little clarification of the basic question. The results together with an appreciation of the possible existence of other unknown factors bearing on poliomyelitis incidence, which might influence to a different extent the participants and non-participants, led certain consultants of the Evaluation Center to suggest that in observed control areas the unvaccinated members of the second grade be combined with the vaccinated population to form the test group for comparison with the combined first and third grade populations as controls. In the tabulations, to follow, this type of comparison is included; however, it was deemed preferable by the staff of the Evaluation Cen-

ter, before analyses were begun, to employ as the control population in observed areas that which was originally announced to the states at the time they enrolled in the study, namely, a comparison of the poliomyelitis experience in vaccinated second grade children with the combined experience in the total first and third grades. It is difficult to combine incidence in vaccinated and unvaccinated populations and have a clear view of the effect in the vaccinated alone.

Other alternative procedures were considered and discarded, such as the use as control that portion of the first and third grades which signified willingness to participate, through submission of a parental consent form. This would seem to be the ideal group for comparison with the vaccinates. Unfortunately, the accuracy of data on participation status of first and third grade children varied greatly from area to area.