CHAPTER 1

SUMMARY OF RESULTS AND CONCLUSIONS

This first chapter presents the essential condensations of data from which the final interpretations and conclusions concerning the 1954 Field Trial of poliomyelitis vaccine (Salk) are drawn. Tables and analyses are arranged in a sequence which proceeds from the identification of the study population through the accumulation of reported cases, their distribution in vaccinated and control subjects and, ultimately, to the critical comparisons from which evaluation of the effect of vaccination in the prevention of poliomyelitis was derived. Succeeding chapters present complete details of the study: how it was formed and how the data were obtained; the efforts to eliminate bias and to obtain uniformity of procedure; the multiple approaches to the establishment of secure diagnosis; the efforts to detect untoward effects; and the reliability of results.

The Field Trial comprised, in fact, two studies conducted at the same time under a single plan for the collection of data. The placebo plan was designed to assure strict comparability between the vaccinated and control subjects. This was done by randomly selecting the two groups from a single volunteering population and by concealing the specific nature of the inoculum which each person received until all data were assembled and final diagnosis had been made for each case. The observed control plan involved the vaccination of an identified segment of the children while others were openly designated as the comparison group. Although administratively simpler, the second procedure has inherent scientific weaknesses. The two studies involved different people in different areas and with different degrees of exposure to poliomyelitis. The data for investigation were acquired from 211 different study areas in 44 states together with some from Canada and Finland. They represent the results obtained not with a single lot of vaccine but with multiple lots of varied potency used in areas where the nature and degree of challenge differed widely. Although the bulwark of confidence resides primarily in the placebo study, parallel analyses of material from observed areas are also presented.

Intensive effort was maintained to assure (1) completeness in registration, (2) accurate records of inoculation, (3) conformity with procedures for the reporting of cases no matter what the prevalence of disease, (4) detailed, objective investigation of cases, and (5) their diagnostic classification under criteria considered by expert advisors to be valid within the limits of diagnostic accuracy. The resultant data possess a high degree of reliability and completeness.

The accumulated information has been subjected to repeated and detailed scrutiny as to its acceptability according to established criteria and for accuracy and consistency in classification. The material has been reviewed in the light of critical queries and later events for evidence which might have been overlooked or misconstrued. Interpretations have been appraised statistically by additional methods and consultants. The final tables, constructed after searching reconsideration of the data, contain certain minor corrections usually occasioned by delayed laboratory reports or other late observations which may have altered diagnosis. Otherwise, the reassembled contents are essentially the same as in the Summary Report.[34]*

The conclusion also remains the same: that properly prepared vaccine of the Salk variety is safe, antigenically potent and has a high degree of effectiveness in the prevention of paralytic poliomyelitis.

* Superior figures indicate reference numbers in the Bibliography.

THE STUDY POPULATION

The total population under observation in the placebo study is shown in Table 1. It is seen that the numbers receiving vaccine and placebo are the same. In fact, even those receiving only partial series of one or the other were numerically equal. Those listed as "Participation Not Requested" represent essentially those who refused to participate while the small percentage called "Participation Not Recorded" represent uninoculated persons who did not request participation but whose record of parents' refusal had not been entered on the forms. The population actually under test, however, is the 401,974 volunteering children of the first, second, and third grades of school who received a complete series of undisclosed material, equally distributed between vaccine and placebo. The comparison of incidence of poliomyelitis in these two equivalent groups is the basis for evaluation of vaccine effect.

Table 1

PARTICIPATION STATUS OF STUDY POPULATION
BY VACCINATION STATUS
PLACEBO AREAS

Participation Status by Vaccination Status	All Grades (1, 2, & 3) Number	Percent
Total	749,236	100.0
Participation Requested	455,474	60.8
Complete Vaccinations	200,745	26.8
Complete Placebo Injections	201,229	26.9
Incomplete Vaccinations	8,484	1.1
Incomplete Placebo Injections	8,577	1.1
Absent or Withdrew	36,439	4.9
Participation Not Requested	280,868	37.5
Participation Not Recorded	12,894	1.7

In the observed control study the total population under observation was also that of the first, second, and third grades of the areas. However, vaccination was offered to only members of the second grade. The designated groups for comparison were the 221,998 children of the second grade who requested and received complete series of vaccine and the 725,173 uninoculated children of the combined first and third grades regardless of whether they had requested participation, indicated refusal or, because of local administrative decisions, were not canvassed. The uninoculated of the second grade either declined, were absent, or changed their minds. (Table 2)

INCIDENCE DURING THE STUDY PERIOD

The official study period was defined in advance to begin two weeks after the third injections were completed in a given area, corresponding to the time when specimens of serum were obtained for the measurement of antibody response. The time was specifically determined for each area but generally was about the middle of June. From then until December 31, 1954, 1,012 cases considered to be poliomyelitis were reported to the Vaccine Evaluation Center (VEC) among the 1,829,916 total population under observation. Of these, 428, or 57 per 100,000, developed in placebo areas and 584, or 54 per 100,000, occurred in observed study areas (Table 3).

Prevalence by Diagnostic Class

Final classification and percent distribution by VEC diagnostic categories are shown in Table 3. From placebo areas 83 percent and from observed areas 86 percent of the cases were accepted as poliomyelitis; of these, 75 percent in placebo areas and 83 percent in observed areas were classified as paralytic.

Table 2

PARTICIPATION STATUS OF STUDY POPULATION
BY VACCINATION STATUS
OBSERVED AREAS

Participation Status by Vaccination Status	All Grades (1, 2, & 3)		2nd Grade		1st and 3rd Grades	
	Number	Percent	Number	Percent	Number	Percent
Total	1,080,680	100.0	355,507	100.0	725,173	100.0
Participation Requested	567,210	52.5	245,895	69.2	321,315	44.3
Complete Vaccinations	221,998	20.5	221,998	62.4		
Incomplete Vaccinations	9,904	0.9	9,904	2.8		
Absent or Withdrew	13,993	1.3	13,993	3.9		
Participation Not Requested	332,870	30.8	105,211	29.6	227,659	31.4
Participation Not Recorded	180,600	16.7	4,401	1.2	176,199	24.3

Table 3

STUDY CASES BY DIAGNOSTIC CLASS
PLACEBO AND OBSERVED AREAS

Diagnostic Class	All Areas		Placebo Areas		Observed Areas	
	Number	Percent	Number	Percent	Number	Percent
Study Cases - Total	1,012	100.0	428	100.0	584	100.0
Poliomyelitis Cases						
Paralytic	682	67.4	267	62.4	415	71.1
Nonparalytic	176	17.4	88	20.6	88	15.1
Doubtful Poliomyelitis	66	6.5	24	5.6	42	7.2
Not Poliomyelitis	88	8.7	49	11.4	39	6.7

The effect of VEC diagnostic criteria upon the diagnosis initially reported from the field on Form FT-6 is seen in Table 4. The major shift occurs in the diagnostically complex group reported to be nonparalytic poliomyelitis; in the final VEC diagnosis, 51 percent of that total was classified as paralytic and 20 percent of it was considered to be doubtful or not poliomyelitis. In contrast, only 4.2 percent of those reported to VEC as paralytic poliomyelitis was classified as nonparalytic, and 5.3 percent as doubtful or not poliomyelitis. The alterations were much the same in placebo and observed areas. The VEC criteria were designed to include in the paralytic category, cases with minimal evidence of paralysis (paralysis with 0 score). The changes from nonparalytic to paralytic fell largely in this range, emphasizing the probability that the detailed muscle examinations detect muscular impairment which might otherwise be overlooked.

Table 4

FIELD DIAGNOSIS (FT-6) COMPARED WITH VEC DIAGNOSIS
PLACEBO AND OBSERVED AREAS

Field Diagnosis Reported on FT-6	Total	Diagnosis Determined at Evaluation Center							
		Non-paralytic Polio-myelitis	Paralytic Poliomyelitis					Doubtful Polio-myelitis	Not Polio-myelitis
			Total	Spi-nal	Bul-bar	Bulbo-spinal	Fatal		
Placebo Areas									
Study Cases - Total	428	88	267	182	14	67	4	24	49
Nonparalytic Poliomyelitis - Total	230	72	113	97	6	10	-	18	27
Paralytic Poliomyelitis - Total	171	10	150	82	8	56	4	2	9
Spinal	83	4	73	62	2	9	-	1	5
Bulbar	39	-	38	2	6	26	4	-	1
Bulbo-spinal	21	1	19	4	-	15	-	-	1
Encephalitic	1	1	-	-	-	-	-	-	-
Not Specified	27	4	20	14	-	6	-	1	2
Suspect Poliomyelitis - Total	19	5	2	2	-	-	-	4	8
Paralytic	1	-	-	-	-	-	-	-	1
Not Specified	18	5	2	2	-	-	-	4	7
Not Classified - Total	2	-	2	1	-	1	-	-	-
Not Poliomyelitis - Total	6	1	-	-	-	-	-	-	5
Observed Areas									
Study Cases - Total	584	88	415	251	25	127	12	42	39
Nonparalytic Poliomyelitis - Total	279	75	149	119	10	20	-	30	25
Paralytic Poliomyelitis - Total	278	9	256	124	15	105	12	7	6
Spinal	134	6	120	90	3	27	-	4	4
Bulbar	67	1	66	4	11	45	6	-	-
Bulbo-spinal	36	-	33	3	1	23	6	2	1
Encephalitic	5	-	4	2	-	2	-	1	-
Not Specified	36	2	33	25	-	8	-	-	1
Suspect Poliomyelitis - Total	17	2	7	5	-	2	-	5	3
Paralytic	-	-	-	-	-	-	-	-	-
Not Specified	17	2	7	5	-	2	-	5	3
Not Classified - Total	4	-	3	3	-	-	-	-	1
Not Poliomyelitis - Total	6	2	-	-	-	-	-	-	4

DISTRIBUTION OF STUDY CASES BY DIAGNOSTIC CLASS AND VACCINATION STATUS

The first table of this series, Table 5, presents the cases in the principle diagnostic categories according to their distribution in all the different segments of the total population under observation in placebo and observed study areas. Group-specific rates per 100,000 are shown. The essential consideration is the comparison of incidence in the vaccinated and the established controls.

In placebo areas the rate and the number of cases of poliomyelitis among the placebo controls were 2.5 times as great as among the vaccinated. This difference is confined almost entirely to paralytic poliomyelitis; there were 33 paralytic cases in the vaccinated and 110 in the placebo controls with corresponding rates of 16 and 55 per 100,000. Thus, there was 3.3 times as much paralytic poliomyelitis in the controls as in the vaccinated, meaning that 77 percent of the paralytic cases arising in the combined test groups occurred in the controls. However, there is no difference between attack rates in the two groups for nonparalytic poliomyelitis nor for doubtful or not poliomyelitis cases.

In the observed control study, there was again no difference in the rates among vaccinated and designated controls for nonparalytic poliomyelitis, doubtful or not poliomyelitis. But the incidence of paralytic poliomyelitis was 2.7 times greater in the observed controls, with 331 cases and a rate of 46, in comparison with 38 cases and a rate of 17 in the vaccinated.

With the number of paralytic cases involved in these test groups the differences are quite significant. They indicate that the effect of vaccine lies primarily in its influence upon the occurrence of paralytic poliomyelitis as defined.

Tables 6 and 7 extend the analysis of cases with respect to vaccination and the character and severity of paralytic involvement. Increasing degrees of peripheral muscular impairment are indicated by the scores. Estimates of the significance of the difference in rates among vaccinated and controls are included. The statistical procedures employed are detailed in the Statistical Methods section, Chapter XVII.

Table 5

DIAGNOSTIC CLASS BY VACCINATION STATUS OF STUDY CASES
PLACEBO AND OBSERVED AREAS

Vaccination Status	Study Population	Total Study Cases		Poliomyelitis						Doubtful Poliomyelitis		Not Poliomyelitis	
				Total		Paralytic		Nonparalytic					
		Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
All Areas - Total	1,829,916	1,012	55	858	47	682	37	176	10	66	4	88	5
Placebo Areas - Total	749,236	428	57	355	47	267	36	88	12	24	3	49	7
Vaccinated	200,745	81	40	56	28	33	16	23	11	10	5	15	7
Placebo	201,229	162	81	138	69	110	55	28	14	7	3	17	8
Incomplete Vaccinations	8,484	2	24	2	24	2	24	-	-	-	-	-	-
Incomplete Placebo Injections	8,577	6	70	6	70	4	47	2	23	-	-	-	-
Not Inoculated	330,201	177	54	153	46	118	36	35	11	7	2	17	5
Observed Areas - Total	1,080,680	584	54	503	47	415	38	88	8	42	4	39	4
Vaccinated	221,998	75	34	55	25	38	17	17	8	12	5	8	4
Controls	725,173	440	61	391	54	331	46	60	8	24	3	25	3
Incomplete Vaccinations	9,904	4	40	4	40	4	40	-	-	-	-	-	-
Second Grade Not Inoculated	123,605	65	53	53	43	42	34	11	9	6	5	6	5

Table 6

DEGREE OF PARALYSIS BY DIAGNOSTIC CATEGORY AND VACCINATION STATUS OF STUDY CASES PLACEBO AREAS

Degree of Paralysis by Diagnostic Category	Number of Cases					Rate per 100,000			
	Total		Vaccinated	Placebo	Other**	Vaccinated	Placebo	S.L.	Other**
	No.	%							
Study Cases - Total	428	100.0	81	162	185	40	81	.001	53
Poliomyelitis Cases - Total	355	82.9	56	138	161	28	69	.001	46
Paralytic - Total	267	62.4	33	110	124	16	55	.001	36
Spinal	182	42.5	28	67	87	14	33	.001	25
Score 0	60	14.0	9	24	27	4	12	.01	8
1-19	43	10.0	9	10	24	4	5	NS	7
20-89	47	11.0	6	20	21	3	10	.01	6
90-199	23	5.4	2	9	12	1	4	.05	3
200+	9	2.1	2	4	3	1	2	NS	1
Bulbar	14	3.3	3	5	6	1	2	NS	2
Bulbo-spinal	67	15.7	2	34	31	1	17	.001	9
Score 0	19	4.4	1	10	8	*	5	.01	2
1-19	20	4.7	-	13	7	-	6	.001	2
20-89	11	2.6	1	5	5	*	2	NS	1
90-199	13	3.0	-	5	8	-	2	.05	2
200+	4	0.9	-	1	3	-	*	NS	1
Fatal	4	0.9	-	4	-	-	2	NS	-
Nonparalytic - Total	88	20.6	23	28	37	11	14	NS	11
Doubtful Poliomyelitis - Total	24	5.6	10	7	7	5	3	NS	2
Not Poliomyelitis - Total	49	11.4	15	17	17	7	8	NS	5

Degree of paralysis in each case determined by muscle examination showing largest score.
* Less than 1 per 100,000.
** See Glossary.
S.L. - Level of statistical significance.
NS - Not significant at level of .05.

It is seen, Table 6, that in placebo areas the level of significance for the difference in total paralytic rates of vaccinated and controls is P = <.001 (variation this great or greater to be expected by chance less than once in 1,000 trials). Despite the fact that there is no difference in nonparalytic rates the significance of difference in paralytic incidence carries over to the total poliomyelitis cases and even further to total reported cases including those which were not poliomyelitis. Of the 33 paralytic cases in the vaccinated, 5, or 15 percent, had bulbar involvement in contrast to 43, or 39 percent, of the paralytic cases in placebo subjects. There is a suggestion that the proportion of the spinal paralytic cases that fell in the two mildest categories of involvement was greater among the vaccinated than in controls, 64 versus 50 percent. If bulbo-spinal cases are considered to be of greater severity, it is striking that only 2 of them appeared in the vaccinated and 34 in the placebo recipients. The 4 fatal cases occurred in controls.

Table 7

DEGREE OF PARALYSIS BY DIAGNOSTIC CATEGORY
AND VACCINATION STATUS OF STUDY CASES
OBSERVED AREAS

Degree of Paralysis by Diagnostic Category	Number of Cases					Rate per 100,000			
	Total		Vaccinated	Controls	Other**	Vaccinated	Controls	S.L.	Other**
	No.	%							
Study Cases - Total	584	100.0	75	440	69	34	61	.001	52
Poliomyelitis Cases - Total	503	86.1	55	391	57	25	54	.001	43
Paralytic - Total	415	71.1	38	331	46	17	46	.001	34
Spinal	251	43.0	20	201	30	9	28	.001	22
Score 0	82	14.0	12	65	5	5	9	NS	4
1-19	65	11.1	5	51	9	2	7	.01	7
20-89	67	11.5	2	53	12	1	7	.001	9
90-199	26	4.5	1	22	3	*	3	.05	2
200+	10	1.7	-	9	1	-	1	NS	1
Unknown	1	0.2	-	1	-	-	*	NS	-
Bulbar	25	4.3	3	20	2	1	3	NS	1
Bulbo-spinal	127	21.7	15	98	14	7	14	.01	10
Score 0	23	3.9	5	15	3	2	2	NS	2
1-19	38	6.5	6	28	4	3	4	NS	3
20-89	33	5.7	4	26	3	2	4	NS	2
90-199	12	2.0	-	10	2	-	1	NS	1
200+	20	3.4	-	18	2	-	2	.01	1
Unknown	1	0.2	-	1	-	-	*	NS	-
Fatal	12	2.1	-	12	-	-	2	.05	-
Nonparalytic - Total	88	15.1	17	60	11	8	8	NS	8
Doubtful Poliomyelitis - Total	42	7.2	12	24	6	5	3	NS	4
Not Poliomyelitis - Total	39	6.7	8	25	6	4	3	NS	4

Degree of paralysis in each case determined by muscle examination showing largest score.
* Less than 1 per 100,000.
** See Glossary.
S.L. - Level of statistical significance.
NS - Not significant at level of .05.

In observed areas the significance of difference in rates of total paralytic and spinal paralytic cases among vaccinated and observed controls was also at the .001 level (Table 7). The rates for spinal paralytic cases were 9 and 28, respectively; only 3 of 20 cases in the vaccinated were in the higher paralytic grades, again suggesting that vaccine effect is more distinct as severity increases. The 2:1 difference between rates for bulbo-spinal cases in vaccinated and controls, although less pronounced than in the placebo study, was significant at the .01 level and none of the vaccinated cases occurred in the two most severe grades of peripheral involvement. Twelve fatal cases of poliomyelitis occurred in control subjects, a case fatality of 3.6 percent in that group.

LABORATORY-POSITIVE CASES

The cases presented in the foregoing tables were classified as poliomyelitis from evidence obtained by clinical examination with or without supporting data from laboratory investigations. Those with well-defined, characteristic findings created little difficulty

Table 8

VIRUS ISOLATION BY SEROLOGY AND VACCINATION STATUS POLIOMYELITIS STUDY CASES PLACEBO AND OBSERVED AREAS

Virus Isolation by Serology	Placebo Areas							Observed Areas						
	Number of Cases			Rate Per 100,000				Number of Cases			Rate Per 100,000			
	Vaccinated	Placebo	Other**	Vaccinated	Placebo	S.L.	Other**	Vaccinated	Controls	Other**	Vaccinated	Controls	S.L.	Other**
Poliomyelitis Cases - Total	56	138	161	28	69	.001	46	55	391	57	25	54	.001	43
Poliomyelitis Virus Isolated from Study Member - Total	15	71	91	7	35	.001	26	19	214	23	9	30	.001	17
Serology: Positive	5	27	26	2	13	.001	7	6	83	9	3	11	.001	7
Probable	1	22	40	*	11	.001	12	5	66	6	2	9	.001	4
Negative	-	-	1	-	-	-	*	-	-	1	-	-	-	1
Indeterminate	7	14	18	3	7	NS	5	6	38	6	3	5	NS	4
Inconsistent	1	1	2	*	*	NS	1	-	6	-	-	1	NS	-
Not Done	1	7	4	*	3	.05	1	2	21	1	1	3	NS	1
Type I Virus Isolated - Total	14	40	51	7	20	.001	15	13	115	8	6	16	.001	6
Serology: Positive	5	11	13	2	5	NS	4	4	49	4	2	7	.01	3
Probable	-	16	24	-	8	.001	7	3	29	2	1	4	.05	1
Negative	-	-	-	-	-	-	-	-	-	1	-	-	-	1
Indeterminate	7	9	9	3	4	NS	3	4	23	-	2	3	NS	-
Inconsistent	1	1	2	*	*	NS	1	-	5	-	-	1	NS	-
Not Done	1	3	3	*	1	NS	1	2	9	1	1	1	NS	1
Type II Virus Isolated - Total	-	6	9	-	3	.05	3	2	36	2	1	5	.01	1
Serology: Positive	-	3	1	-	1	NS	*	2	10	2	1	1	NS	1
Probable	-	2	6	-	1	NS	2	-	17	-	-	2	.01	-
Negative	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Indeterminate	-	-	1	-	-	-	*	-	5	-	-	1	NS	-
Inconsistent	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not Done	-	1	1	-	*	NS	*	-	4	-	-	1	NS	-
Type III Virus Isolated - Total	1	25	31	*	12	.001	9	4	63	13	2	9	.001	10
Serology: Positive	-	13	12	-	6	.001	3	-	24	3	-	3	.01	2
Probable	1	4	10	*	2	NS	3	2	20	4	1	3	NS	3
Negative	-	-	1	-	-	-	*	-	-	-	-	-	-	-
Indeterminate	-	5	8	-	2	.05	2	2	10	6	1	1	NS	4
Inconsistent	-	-	-	-	-	-	-	-	1	-	-	*	NS	-
Not Done	-	3	-	-	1	NS	-	-	8	-	-	1	NS	-
Poliomyelitis Virus Isolated from Family Member - Total	-	5	4	-	2	.05	1	1	9	1	*	1	NS	1
Type I Virus Isolated - Total	-	2	2	-	1	NS	1	1	6	1	*	1	NS	1
Serology: Positive	-	-	1	-	-	-	*	1	3	-	*	*	NS	-
Probable	-	1	-	-	*	NS	-	-	1	-	-	*	NS	-
Negative	-	-	1	-	-	-	*	-	-	-	-	-	-	-
Indeterminate	-	-	-	-	-	-	-	-	1	1	-	*	NS	1
Inconsistent	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not Done	-	1	-	-	*	NS	-	-	1	-	-	*	NS	-
Type II Virus Isolated - Total	-	1	-	-	*	NS	-	-	1	-	-	*	NS	-
Serology: Positive	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Probable	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Negative	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Indeterminate	-	-	-	-	-	-	-	-	1	-	-	*	NS	-
Inconsistent	-	1	-	-	*	NS	-	-	-	-	-	-	-	-
Not Done	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Type III Virus Isolated - Total	-	2	2	-	1	NS	1	-	2	-	-	*	NS	-
Serology: Positive	-	1	-	-	*	NS	-	-	-	-	-	-	-	-
Probable	-	-	1	-	-	-	*	-	1	-	-	*	NS	-
Negative	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Indeterminate	-	1	1	-	*	NS	*	-	-	-	-	-	-	-
Inconsistent	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not Done	-	-	-	-	-	-	-	-	1	-	-	*	NS	-

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* Less than 1 per 100,000.
** See Glossary.
S.L. - Level of statistical significance.
NS - Not significant at level of .05.

Table 8 (Continued)

Virus Isolation by Serology	Placebo Areas							Observed Areas						
	Number of Cases			Rate Per 100,000				Number of Cases			Rate Per 100,000			
	Vaccinated	Placebo	Other**	Vaccinated	Placebo	S.L.	Other**	Vaccinated	Controls	Other**	Vaccinated	Controls	S.L.	Other**
Other Virus Isolated from Study Member - Total	11	22	27	5	11	.05	8	3	9	-	1	1	NS	-
Serology: Positive	-	2	1	-	1	NS	*	-	-	-	-	-	-	-
Type I	-	1	1	-	*	NS	*	-	-	-	-	-	-	-
Type II	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Type III	-	1	-	-	*	NS	-	-	-	-	-	-	-	-
Probable	2	6	8	1	3	NS	2	1	5	-	*	1	NS	-
Type I	1	2	4	*	1	NS	1	-	1	-	-	*	NS	-
Type II	1	2	2	*	1	NS	1	-	2	-	-	*	NS	-
Type III	-	2	2	-	1	NS	1	1	2	-	*	*	NS	-
Negative	-	1	-	-	*	NS	-	-	-	-	-	-	-	-
Indeterminate	9	6	14	4	3	NS	4	2	4	-	1	1	NS	-
Not Done	-	7	4	-	3	.01	1	-	-	-	-	-	-	-
No Virus Isolated from Study Member - Total	24	24	26	12	12	NS	7	30	100	19	14	14	NS	14
Serology: Positive	3	6	5	1	3	NS	1	3	29	4	1	4	.05	3
Type I	1	1	2	*	*	NS	1	2	13	-	1	2	NS	-
Type II	1	2	-	*	1	NS	-	1	4	1	*	1	NS	1
Type III	1	3	3	*	1	NS	1	-	12	3	-	2	.05	2
Probable	4	13	11	2	6	.05	3	2	32	6	1	4	.01	4
Type I	2	7	6	1	3	NS	2	-	9	4	-	1	NS	3
Type II	1	3	4	*	1	NS	1	1	10	1	*	1	NS	1
Type III	1	3	1	*	1	NS	*	1	13	1	*	2	NS	1
Negative	1	-	1	*	-	NS	*	-	-	-	-	-	-	-
Indeterminate	15	5	8	7	2	NS	2	25	35	9	11	5	NS	7
Not Done	1	-	1	*	-	NS	*	-	4	-	-	1	NS	-
Specimen Not Collected or Not Tested - Total	6	16	13	3	8	.05	4	2	59	14	1	8	.001	10
Serology: Positive	1	5	2	*	2	NS	1	1	4	1	*	1	NS	1
Type I	-	3	2	-	1	NS	1	-	1	1	-	*	NS	1
Type II	1	-	-	*	-	NS	-	1	1	-	*	*	NS	-
Type III	-	2	-	-	1	NS	-	-	2	-	-	*	NS	-
Probable	-	2	3	-	1	NS	1	1	19	2	*	3	.05	1
Type I	-	1	3	-	*	NS	1	1	9	1	*	1	NS	1
Type II	-	-	-	-	-	-	-	-	6	-	-	1	NS	-
Type III	-	1	-	-	*	NS	-	-	4	1	-	1	NS	1
Negative	-	-	-	-	-	-	-	-	1	-	-	*	NS	-
Indeterminate	3	3	4	1	1	NS	1	-	16	2	-	2	.05	1
Not Done	2	6	4	1	3	NS	1	-	19	9	-	3	.01	7

but a degree of uncertainty persists regarding a significant proportion of cases, especially in the milder classes, when supporting laboratory data were not available. The prevalence, during the study period, of illness resembling mild poliomyelitis from which unidentified orphan viruses were obtained, increased the difficulty in some areas. It could not be uniformly ascertained whether the illnesses were infections with the unknown viruses or whether the illness was caused by an undetected poliomyelitis virus and the orphan virus represented a sub-clinical, incidental infection, or vice versa. Recovery of poliomyelitis virus from the stool of a patient with clinical poliomyelitis was, however, accepted as prima-facie evidence that the disease was poliomyelitis. It was well recognized, nevertheless, from the data accumulated under the conditions of the Field Trial that failure to recover virus from the stool did not eliminate a diagnosis of poliomyelitis.

Complete summaries of the cases in relation to virus isolation and serology are presented in Table 8.

Poliomyelitis virus was isolated from 319 of the cases occurring in the vaccinated and control subjects. The distribution of virus-positive poliomyelitis cases by type of virus is shown in the following table:

VIRUS-POSITIVE POLIOMYELITIS CASES BY VIRUS TYPE AND VACCINATION STATUS PLACEBO AND OBSERVED AREAS

Area by Vaccination Status	Total	Poliomyelitis Virus Isolated		
		Type I	Type II	Type III
Placebo and Observed Areas - Total	319	182	44	93
Percent	100	57	14	29
Placebo Areas - Total	86	54	6	26
Vaccinated	15	14	-	1
Placebo	71	40	6	25
Observed Areas - Total	233	128	38	67
Vaccinated	19	13	2	4
Controls	214	115	36	63

Source: Table 8.

The incidence rate of virus-positive cases was 7 in the vaccinated and 35 in the controls of placebo areas; 9 in the vaccinated and 30 in the controls of observed areas (Table 8). Again these are highly significant differences. In both studies the rates for the nonparticipating "other" group were somewhat less than those for the controls. Virus was recovered from a distinctly smaller proportion of vaccinated cases than from the controls or others.

It should be noted here that, in total, only 36 percent of the virus-positive cases had clear-cut, positive serological tests but that essentially an equal proportion of the total cases had "probable" serology, which means that they had antibody only to the specific virus recovered from the stool; hence, these results also possess high diagnostic significance. The serological responses are discussed fully in Chapter VI, Diagnostic Criteria.

Table 9 presents the frequency of recovery of poliomyelitis virus from the stools of patients in the various diagnostic groups. Stool specimens from 738, 88 percent, of 842 non-fatal cases of poliomyelitis were tested and poliomyelitis virus was recovered from 426, or 58 percent. Specimens were tested from 89 percent of patients called paralytic poliomyelitis in placebo areas and from 85 percent in observed areas; poliomyelitis virus was found in 64 percent of those tested. The frequency was greater in bulbo-spinal than in spinal paralytic cases. Virus was isolated from only 37 percent of the non-paralytic cases tested in both studies.

In addition to the 426 non-fatal virus-positive poliomyelitis cases, there were 73

Table 9

POLIOMYELITIS VIRUS ISOLATIONS FROM CASE SPECIMENS TESTED FOR STUDY CASES BY DIAGNOSTIC CATEGORY PLACEBO AND OBSERVED AREAS

Diagnostic Category	Placebo Areas				Observed Areas			
	Total Cases	Case Specimens Tested			Total Cases	Case Specimens Tested		
		Total	Poliomyelitis Virus Isolations			Total	Poliomyelitis Virus Isolations	
			Number	Percent			Number	Percent
Study Cases - Total	428	382	177	46	584	489	256	52
Poliomyelitis Cases - Total	355	320	177	55	503	428	256	60
Paralytic - Total	267	238	150	63	415	352	225	64
Spinal	182	165	100	61	251	213	126	59
Bulbar	14	13	9	69	25	20	13	65
Bulbo-spinal	67	57	39	68	127	112	81	72
Fatal	4	3	2	67	12	7	5	71
Nonparalytic - Total	88	82	27	33	88	76	31	41
Doubtful Poliomyelitis and Not Poliomyelitis - Total	73	62	0	-	81	61	0	-

serologically-positive cases and 10 which were neither virus-positive nor serologically-positive but which were in families where poliomyelitis virus was isolated from a family member. All of these 509 combined were then considered laboratory-positive or confirmed cases of poliomyelitis. They constitute 60 percent of the total non-fatal cases of poliomyelitis reported from both placebo and observed areas.

Analysis, therefore, turned to the laboratory-proved cases of poliomyelitis, a group in which the reliability of diagnosis is high. Recognized orphan virus infections are hereby excluded. There was again no significant difference between vaccinated and placebo groups in terms of nonparalytic cases (Table 10). The rate for total paralytic cases in the placebo controls was 38 and 6 in the vaccinated, a 6-fold difference; the rate in controls was 5.5 times greater for spinal paralytics and 12 times greater for the bulbo-spinal cases.

In observed areas, the same trend was noted (Table 11). The rate for total paralytic cases was 4.4 times greater in the designated controls than in the vaccinated; that for spinal paralytic cases was 6 times greater. The distinction between rates for bulbo-spinal cases was only 2.5:1 in comparison with a much greater differential in the placebo study.

Comparison of Tables 6-7 with Tables 10-11 shows that the incidence of non-laboratory-positive paralytic cases was essentially the same in the vaccinated, placebo, and uninoculated. Thus their removal results in a proportionately greater incidence of laboratory-positive paralytic poliomyelitis in the controls and others than in the vaccinated. Confidence in the clinical diagnosis of poliomyelitis improves when paralysis is demonstrable. If this is combined with supporting laboratory evidence of infection with a specific poliomyelitis virus, diagnosis becomes firmly established. The foregoing data show that under these conditions the preventive influence of vaccine stands out more clearly, unobscured by diagnostic uncertainties.

Table 10

LABORATORY POSITIVE STUDY CASES BY DEGREE OF PARALYSIS, DIAGNOSTIC CATEGORY, AND VACCINATION STATUS PLACEBO AREAS

Degree of Paralysis by Diagnostic Category	Number of Cases				Rate per 100,000			
	Total	Vaccinated	Placebo	Other***	Vaccinated	Placebo	S.L.	Other***
Laboratory Positive** Poliomyelitis - Total	209	19	88	102	9	44	.001	29
Nonparalytic - Total	34	6	11	17	3	5	NS	5
Paralytic - Total	175	13	77	85	6	38	.001	24
Spinal - Total	112	9	45	58	4	22	.001	17
Score 0	25	1	10	14	*	5	.01	4
1-19	21	1	6	14	*	3	NS	4
20-89	38	3	17	18	1	8	.01	5
90-199	19	2	8	9	1	4	NS	3
200+	9	2	4	3	1	2	NS	1
Bulbar - Total	10	2	4	4	1	2	NS	1
Bulbo-spinal - Total	50	2	25	23	1	12	.001	7
Score 0	13	1	7	5	*	3	.05	1
1-19	15	-	10	5	-	5	.001	1
20-89	10	1	4	5	*	2	NS	1
90-199	8	-	3	5	-	1	NS	1
200+	4	-	1	3	-	*	NS	1
Fatal - Total	3	-	3	-	-	1	NS	-

Degree of paralysis in each case determined by muscle examination showing largest score.

* Less than 1 per 100,000.

** Includes: a. Cases with poliomyelitis virus isolated from case and typed, regardless of serology (177).

b. Cases with no poliomyelitis virus isolated from case or family member, but with a fourfold or greater rise in antibody titer to one type of virus only (25).

c. Cases with poliomyelitis virus isolated from a family member, provided the serology for the case is not inconsistent with the virus isolated from the family member (7).

*** See Glossary.

S.L. - Level of statistical significance.

NS - Not significant at level of .05.

Table 11

LABORATORY POSITIVE STUDY CASES BY DEGREE OF PARALYSIS, DIAGNOSTIC CATEGORY, AND VACCINATION STATUS OBSERVED AREAS

Degree of Paralysis by Diagnostic Category	Number of Cases				Rate per 100,000			
	Total	Vaccinated	Controls	Other***	Vaccinated	Controls	S.L.	Other***
Laboratory Positive** Poliomyelitis - Total	309	24	256	29	11	35	.001	22
Nonparalytic - Total	41	8	31	2	4	4	NS	1
Paralytic - Total	268	16	225	27	7	31	.001	20
Spinal - Total	156	6	132	18	3	18	.001	13
Score 0	38	2	34	2	1	5	.01	1
1-19	37	1	32	4	*	4	.01	3
20-89	51	2	41	8	1	6	.001	6
90-199	23	1	19	3	*	3	.05	2
200+	7	-	6	1	-	1	NS	1
Bulbar - Total	18	1	16	1	*	2	NS	1
Bulbo-spinal - Total	88	9	71	8	4	10	.01	6
Score 0	14	2	10	2	1	1	NS	1
1-19	26	4	20	2	2	3	NS	1
20-89	22	3	18	1	1	2	NS	1
90-199	11	-	9	2	-	1	NS	1
200+	15	-	14	1	-	2	.05	1
Fatal - Total	6	-	6	-	-	1	NS	-

Degree of paralysis in each case determined by muscle examination showing largest score.

* Less than 1 per 100,000.

** Includes: a. Cases with poliomyelitis virus isolated from case and typed, regardless of serology (256).

b. Cases with no poliomyelitis virus isolated from case or family member, but with a fourfold or greater rise in antibody titer to one type of virus only (42).

c. Cases with poliomyelitis virus isolated from a family member, provided the serology for the case is not inconsistent with the virus isolated from the family member (11).

*** See Glossary.

S.L. - Level of statistical significance.

NS - Not significant at level of .05.

Table 12

VIRUS-POSITIVE PARALYTIC AND NONPARALYTIC POLIOMYELITIS STUDY CASES BY TYPE OF VIRUS ISOLATION AND VACCINATION STATUS PLACEBO AND OBSERVED AREAS

Type of Virus by Diagnostic Class	Number of Cases				Rate Per 100,000			
	Total	Vaccinated	Controls	Other**	Total	Vaccinated	Controls	Other**
Placebo Areas								
Virus Positive Poliomyelitis Study Cases - Total	177	15	71	91	24	7	35	26
Paralytic	150	11	62	77	20	5	31	22
Nonparalytic	27	4	9	14	4	2	4	4
Type I Virus - Total	105	14	40	51	14	7	20	15
Paralytic	88	10	35	43	12	5	17	12
Nonparalytic	17	4	5	8	2	2	2	2
Type II Virus - Total	15	-	6	9	2	-	3	3
Paralytic	12	-	4	8	2	-	2	2
Nonparalytic	3	-	2	1	*	-	1	*
Type III Virus - Total	57	1	25	31	8	*	12	9
Paralytic	50	1	23	26	7	*	11	7
Nonparalytic	7	-	2	5	1	-	1	1
Observed Areas								
Virus Positive Poliomyelitis Study Cases - Total	256	19	214	23	24	9	30	17
Paralytic	225	14	190	21	21	6	26	16
Nonparalytic	31	5	24	2	3	2	3	1
Type I Virus - Total	136	13	115	8	13	6	16	6
Paralytic	119	8	104	7	11	4	14	5
Nonparalytic	17	5	11	1	2	2	2	1
Type II Virus - Total	40	2	36	2	4	1	5	1
Paralytic	33	2	29	2	3	1	4	1
Nonparalytic	7	-	7	-	1	-	1	-
Type III Virus - Total	80	4	63	13	7	2	9	10
Paralytic	73	4	57	12	7	2	8	9
Nonparalytic	7	-	6	1	1	-	1	1

* Less than 1 per 100,000.
** See Glossary.

VIRUS-POSITIVE CASES

If consideration is then turned to the cases from whom specifically identified poliomyelitis virus was recovered, the differences between vaccinated and controls can be examined according to the type of virus concerned.

In the placebo study there were 11 virus-positive paralytic cases in the vaccinated and 62 in placebo controls with corresponding rates of 5 and 31 (Table 12). Ten of the 11 paralytic cases in the vaccinated were associated with Type I virus while 35 occurred in the controls. In the vaccinated there was no paralytic case with Type II recovery and only 1 Type III, in comparison with 4 Type II and 23 Type III cases in the placebo group. These differences are of high significance but it is apparent that the effect of vaccination against paralytic disease caused by Type I virus was less marked than its effect against the other two types. There was little difference in rates for nonparalytic cases; all 4 cases occurring in the vaccinated were related to Type I while there were 5 Type I, 2 Type II, and 2 Type III nonparalytic cases in the controls.

The data from the observed study point out (Table 12) that when measured by comparison of rates for total virus-positive paralytic cases the differences between vaccinated and observed controls are, as in previous analyses, less than in the placebo study. They were 6 and 26, respectively. The smallest margin here, too, relates to Type I cases although 2 Type II and 4 Type III cases were noted among the vaccinated. The rates and distribution of the nonparalytic cases were the same as in the placebo study.

ESTIMATES OF EFFECTIVENESS OF VACCINE

The numerous examinations and analyses subsequently conducted with the data have resulted in no essential change in the estimates of effectiveness which were presented in the Summary Report. The data are firm; they have been collected, handled and interpreted as objectively and honestly as our concentrated efforts could effect. The results represent those derived from comparisons of the vaccinated with the controls. Consequently, the summary presented in the original report is reproduced here in almost the same form with the exception that minor changes in numbers are made. For the sake of clarity, a few lines have been added to Summary Report Table 10, revised as Table 13, to include totals where they were not previously given. Moreover, in addition to estimates of effectiveness based on all virus-positive cases, separate estimates for the virus-positive paralytic cases which were previously not separated are presented for each virus type.

The differences observed between the incidence of poliomyelitis in vaccinated and control subjects are shown through the four different stages of analysis each of which serves progressively to eliminate certain cases which might be considered less conclusively established as poliomyelitis. Tests for significance of the differences between the test groups and estimates of the effectiveness of vaccine as measured in the successive stages were computed by use of the binomial theory as described in the Statistical Methods Chapter. Sections of the following discussion are numbered for convenient reference to the stages of analysis as shown in Table 13.

1. As a first stage, the data comprising the total cases reported, total cases of poliomyelitis, total nonparalytic, and total paralytic in both placebo and observed control areas were subjected to examination. Through these steps of diagnostic clarification there is a progressive increase in the percentage of effectiveness. There was, however, no significant difference at any stage of analysis in the occurrence of nonparalytic cases in the test groups. When they and the cases considered not to be poliomyelitis are removed so that paralytic cases only remain, an estimate of 70 percent effectiveness is obtained in the placebo areas and 62 percent in the observed areas.

Table 13

ESTIMATES OF EFFECTIVENESS OF VACCINE AT SUCCESSIVE STAGES OF ANALYSIS*

Stage of Analysis	Placebo Study Areas					Observed Study Areas					Source of Data
	Number of Cases		S.L.	Percent Effectiveness		Number of Cases		S.L.	Percent Effectiveness		
	Vaccinated	Placebo		Estimate	Lower Limit	Vaccinated	Controls		Estimate	Lower Limit	Table
Stage 1											
Reported Study Cases	81	162	<.001	50	37	75	440	<.001	44	31	5
Poliomyelitis Cases	56	138	<.001	59	47	55	391	<.001	54	41	
Nonparalytic Cases	23	28	NS	18	<0	17	60	NS	7	<0	
Paralytic Cases	33	110	<.001	70	57	38	331	<.001	62	50	
Stage 2											
Paralytic Spinal Cases	28	67	<.001	58	39	20	201	<.001	67	51	6 and 7
Bulbo-spinal Cases	2	34	<.001	94	79	15	98	<.01	50	18	
Stage 3											
Laboratory Confirmed Paralytic Cases	13	77	<.001	83	72	16	225	<.001	77	64	10 and 11
Spinal	9	45	<.001	80	63	6	132	<.001	85	70	
Bulbo-spinal	2	25	<.001	92	73	9	71	<.01	59	23	
Stage 4											
Virus Positive Poliomyelitis Cases	15	71	<.001	79	65	19	214	<.001	71	56	12
Type I	14	40	<.001	65	39	13	115	<.001	63	38	
Type II	-	6	<.05	100	33	2	36	<.01	82	38	
Type III	1	25	<.001	96	79	4	63	<.001	79	51	
Virus Positive Paralytic Cases	11	62	<.001	82	68	14	190	<.001	76	61	12
Type I	10	35	<.001	71	46	8	104	<.001	75	54	
Type II	-	4	NS	100	<0	2	29	<.05	77	23	
Type III	1	23	<.001	96	76	4	57	<.001	77	45	
Study Population	200,745	201,229				221,998	725,173				

For detailed definitions of S.L., estimate of effectiveness and lower limit, see Statistical Methods Chapter.

* Because of small numbers the bulbar and fatal cases are not shown separately but are included in the totals; all fatal poliomyelitis occurred in controls.

S.L. - Level of statistical significance.

NS - Not significant at level of .05.

2. Because the data indicate that the cases classified as bulbo-spinal paralytic are somewhat more definite clinically and yield a higher percentage of virus recoveries, the second stage was to separate the spinal paralytic cases from the bulbo-spinal. The number of pure bulbar cases was too small to work with properly. In placebo areas effectiveness calculated against spinal paralytic cases was 58 percent with a lower limit of 39 percent; against the bulbo-spinal patients it was 94 percent with a lower limit of 79 percent - an extremely successful effect. In observed areas the calculated effectiveness was about the same against the spinal cases but only 50 percent, with a lower limit of 18, in the bulbo-spinal group. These variations emphasize the influence of small numbers in addition to any differences in severity of risk among placebo and observed study populations.

3. Because the group classified as paralytic poliomyelitis, especially in the mild grades, may contain cases which are not related to poliomyelitis virus, the next tests were conducted with cases which had been demonstrated by laboratory studies to have undergone infection with poliomyelitis virus. They represented a higher degree of confidence in diagnosis. The estimated effectiveness of vaccination in terms of total laboratory-confirmed paralytic cases was 83 percent in placebo areas and 77 percent in observed areas with lower limits of 72 and 64, respectively. The cases were again divided into spinal and bulbo-spinal groups. The effectiveness of vaccine measured against the incidence of spinal paralytic cases was about the same in placebo and observed areas, 80 and 85 percent, respectively, and the corresponding lower limits of estimated effect were 63 and 70, respectively. Enforcement of laboratory criteria apparently eliminated a substantial number of cases which were less influenced by vaccination and which, in reality, may not have been poliomyelitis cases. As in the preceding analysis, the effectiveness measured by bulbo-spinal cases in placebo areas was quite high, 92 percent, but in observed areas it was 59 percent and the significance of difference between vaccinated and control groups was less ($<.01$) but still quite firm.

4. The fourth stage was to estimate the effectiveness of vaccine using all cases from whom a specifically identified type of poliomyelitis virus was recovered. Cases confirmed by serological test alone were not included. In this manner the effectiveness of vaccine against infection with the different types of virus could be evalulated. In placebo areas effectiveness of 79 percent was estimated for total virus-positive poliomyelitis cases; for the individual types the estimated effectiveness was 65 percent against Type I, 100 percent with $<.05$ significance against Type II, and 96 percent against Type III. Since no difference in rates of nonparalytic cases is demonstrable in any compilation, only virus-positive paralytic cases were then considered. The estimated effectiveness of vaccine in this group was 82 percent and against Type I cases was 71 percent.

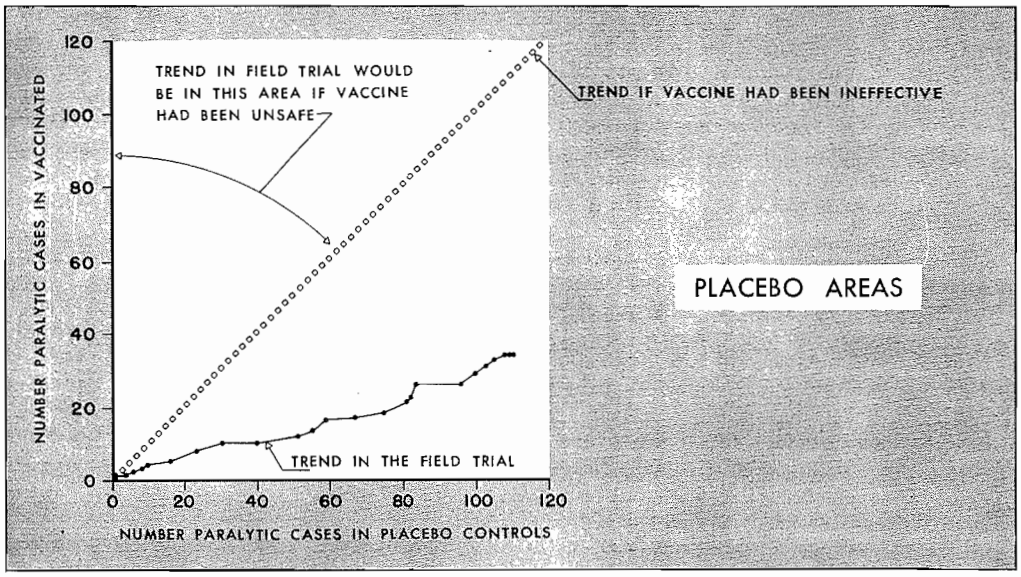
   In observed areas the effectiveness estimated against total virus-positive cases, and against the specific types of virus was somewhat lower than in placebo areas. This tendency exists in the virus-positive paralytic cases as well but in both the total and paralytic groups the estimated effect against the dominant Type I virus was essentially the same as in the placebo series.

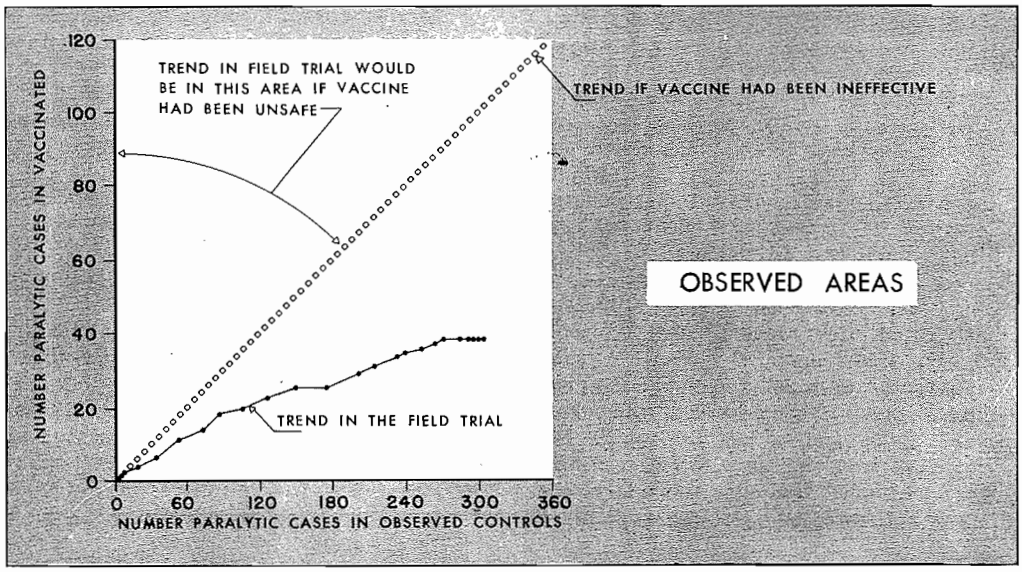
The data represent the composite results obtained with various lots of vaccine used in the different studies. A measure of the effectiveness of different lots of vaccine is discussed in Chapter VIII, Antigenic Potency. Because of the variations both in risk and in antigenic potency the figures presented here are in effect the summation of the influence of lots of quite different degrees of potency. These variations in degree of potency apply to different antigenic components within the lots as well as to lots in their entirety. From these data, it is not possible to select a single

Figure 1

TREND OF PARALYTIC POLIOMYELITIS CASES AMONG VACCINATED CHILDREN AND THEIR CONTROL GROUPS

JUNE 19, 1954 - DECEMBER 31, 1954





value of estimated effectiveness which applies uniformly to all lots of vaccine.

If the data from observed areas are used they indicate that in the aggregate the vaccine preparations employed in those areas were effective in a range of 60 to 80 percent in prevention of paralytic poliomyelitis; the effect was more distinct against spinal paralytic cases than against bulbo-spinal cases. This estimate increases from 62 percent for paralytic cases as a whole to 77 and 76 percent when only the laboratory-confirmed and virus-positive cases are considered. When total virus-positive cases, paralytic and nonparalytic, are examined together, an effectiveness of about 60 percent is observed against disease related to Type I poliomyelitis virus and about 80 percent against Types II and III. If only the virus-positive paralytic cases are used, however, an effectiveness of approximately 76 percent is seen against each of the three types. No influence upon the comparative incidence of nonparalytic poliomyelitis was observed.

It has been repeatedly emphasized that there is greater confidence in the data accumulated from the placebo study areas where comparisons can be made between the strictly controlled, almost identical, test populations observed under conditions of concealed vaccination status which would avoid bias. There was no significant difference in the incidence of nonparalytic poliomyelitis in this series. The estimated effectiveness against paralytic poliomyelitis as a class, whether in terms of total reported cases, laboratory-confirmed or virus-positive, was higher in the placebo study than in the observed areas. The effectiveness measured against spinal paralytic poliomyelitis was slightly less than in observed areas but the effectiveness against bulbo-spinal paralytic disease was much greater in the placebo study.

As discussed earlier the greatest security with respect to diagnosis of poliomyelitis resides in the laboratory-confirmed, or virus-positive paralytic cases. These data from the placebo study areas are, therefore, the most reliable with which to gauge the preventive effect of the vaccine preparation employed. On this basis an estimate of 80 to 90 percent effectiveness against paralytic poliomyelitis is obtained; and this estimate carries a high degree of confidence. Vaccine, as used, was 60 to 70 percent effective in prevention of Type I virus-positive paralytic cases and 90 percent or more effective against paralytic cases of Types II and III poliomyelitis. In some respects the data may represent much less than the maximal effect which could be obtained with uniformly potent lots or with other schedules of administration because a good proportion of the failures in vaccinated persons were individuals whose serological tests demonstrated that the vaccine had not induced adequate antibody responses.

FACTORS AFFECTING THE RESULTS

The following comments are brief summaries of certain factors which have been carefully studied for information as to their possible influence upon the data and the conclusions.

NATURE OF CASES IN THE VACCINATED

The careful and repeated considerations of the cases occurring in vaccinated has given no indication that vaccine incited poliomyelitis in the 1954 study population (Reactions and Provocation, Chapter X). This conclusion is supported by the absence in 1954 of the associated disease phenomena which were readily detectable in 1955. The small number of cases in vaccinated persons, the lack of correlation between site of paralysis and inoculation, the absence of association in time between vaccination and prevalence, the absence of any extension in families or in uninoculated persons in the same schoolroom, lead uniformly to this conclusion. The problem of diagnostic accuracy exists in the cases among vaccinated particularly since a disproportionate number of them fall in the mildest category of paralysis. And there are

definite reasons why some of these cases could reasonably be dismissed because of lack of virus recovery and serological responses. These difficulties are, however, obviated by use of the laboratory-positive or virus-positive cases which provide greater diagnostic assurance. Confusion with orphan virus infections is largely removed as well by the procedure. It eliminates a greater proportion of paralytic cases in the vaccinated than in the controls because virus was recovered with less frequency from the former. Examination of the data concerning individual cases again shows no accumulation by lots of vaccine except as the lot is seen to be antigenically defective. This is contrary to what would be expected if active virus were present. And it is in this respect that the majority of cases among the vaccinated stand out as examples of persons with inadequate antibody response to reported vaccination. It seems certain that had better vaccine been uniformly distributed the results would have been more striking.

QUESTION OF PROVOCATION

The data show the complete similarity between vaccinated and placebo controls of the study population and the difference of the uninoculated "others" (see Glossary) from these two groups. The others had lower rates of incidence than the controls in every diagnostic category in both the observed and placebo studies. Certain reviewers, using the refusals as the controls, a scientifically unjustifiable procedure, suggested that the difference between the rates in others and specific placebo controls might be the result of provocation of paralysis by the placebo injections. This possibility was considered eliminated by the data presented in the Summary Report. It has, however, been carefully studied and re-studied as shown in the chapter covering Provocation. The absence of any significant aggregation of cases with relation to the time of inoculation, the lack of any evidence of selective localization of paralysis, and the similarity in paralytic rates among the refusals relative to those in placebo controls and uninoculated observed controls give finality to the discarding of any assumption that paralysis was provoked by the placebo injection.

ANTIGENIC POTENCY AND EFFECTIVENESS

The study demonstrated a definite correlation between the potency of vaccine preparations, measured by the antibody response of recipients, and the protective effect. The Type I response in vaccinated subjects as a whole was decidedly less than that to Type II or III antigen. In most lots which exhibited a difference in antigenic potency of the constituent antigens, the Type I component was most likely to be defective. On the basis of earlier incomplete data an attempt was made to classify lots in broad categories of antigenic potency; subsequent data have generally been in support of the earlier conclusions. When the lots are then viewed for relation between antigenic potency and estimated protective effect there is, generally, agreement between the two measurements. When the areas in which a lot was used provided a reasonable challenge, it was seen that for each lot which had a defined antigenic effect of 75 percent or more per type component there were no reported cases of paralytic poliomyelitis of the specified type among its vaccinated subjects. Nevertheless, a lot such as 302 was quite deficient in the Type I antigen but was used primarily in areas where Type III virus was dominant against which it was quite effective. In two other instances lots which appeared to be of only moderate antigenic potency were quite effective. Lot 507 was essentially inert antigenically and it is not clear how it ever got through the screening tests. Lot 304, on the other hand, was very good in each antigen and was of the potency which all vaccine should reach; there is little doubt that if this level of potency had been uniformly maintained in all preparations used in the Field Trial a still greater preventive effect would have been observed. A large proportion of the cases reported in vaccinated persons was demonstrated by serological procedures to have inadequate

complements of antibody, thereby showing that the vaccine or the response or both were unsatisfactory in those specific instances.

This entire subject is presented with detailed analysis in the Antigenic Response section of Chapter VIII.

AGE

In contrast to the distinct protective effects of vaccine in the other age groups, no significant difference was seen between vaccinated and placebo controls of 6 years of age. There were 16 paralytic cases in the vaccinated and 23 in the controls. Efforts to explain the aberration are discussed in the chapter dealing with Age and Sex. There is no evidence that the failure is related to differences between 6-, 7-, and 8-year-olds in antibody prevalence prior to vaccination or in their responsiveness to vaccine. There was a disproportionate incidence of orphan virus infections in the 6-year-olds. If poliomyelitis virus-positive cases alone are considered it is apparent that the defect lay with Type I antigen since all such cases in the vaccinated of placebo areas were Type I. There were 7 cases due to Types II and III in the controls but none in the vaccinated. However, the greatest deviation seems to be less an excess of cases in the 6-year-old vaccinated than a distinct deficit in cases among the 6-year-old controls. The true explanation may be a mixture of all these influences working in the realm of small numbers.

ORPHAN VIRUS INFECTIONS

The orphan virus infections earlier mentioned created difficulties of interpretation. Their nature is discussed in detail in a later section and here the term is used to include all unidentified viruses. Among the 428 total cases reported in placebo areas orphan viruses were recovered from 83, and 60 of these, on the basis of clinical examinations, were classified as poliomyelitis, despite the reported presence of an orphan virus. Their distribution among the study segments had no order. In the analyses which consider only cases which were laboratory-confirmed for poliomyelitis, or poliomyelitis virus-positive, orphan virus cases are largely avoided or eliminated. Their influence upon the total accumulations by diagnosis is seen in Tables 14 and 15 from which the orphan virus cases are removed in comparison with Tables 6 and 7. Of the 60 such cases listed by VEC as poliomyelitis 34 were called paralytic; 18 of the latter fell in the minimal paralytic group and 13 in the second mildest grade. They also contributed 26 of the 88 cases classified as nonparalytic poliomyelitis. Their removal, therefore, increased the percentage of paralytic cases in the remaining group and decreased the percentage of nonparalytic. The rates in all categories of poliomyelitis consequently declined, and in making estimates of effectiveness of vaccine the absence of the orphan virus cases tends to give a slight but uniform increase in numerical values.

In observed areas (Table 15) only 23 cases associated with orphan viruses were reported. The agents were much more diversified in character without concentration in any area. Ten of the cases had been called paralytic poliomyelitis. The removal of these cases had little influence upon categorical rates in any respect.

Table 14

DEGREE OF PARALYSIS BY DIAGNOSTIC CATEGORY AND VACCINATION STATUS OF STUDY CASES (EXCLUDING ORPHAN VIRUS CASES) PLACEBO AREAS

Degree of Paralysis by Diagnostic Category	Number of Cases					Rate per 100, 000			
	Total		Vaccinated	Placebo	Other**	Vaccinated	Placebo	S. L.	Other**
	Number	Percent							
Study Cases - Total	345	100.0	59	133	153	29	66	.001	44
Poliomyelitis Cases - Total	295	85.5	45	116	134	22	58	.001	39
Paralytic - Total	233	67.5	27	97	109	13	48	.001	31
Spinal	152	44.1	22	56	74	11	28	.001	21
Score 0	44	12.8	6	16	22	3	8	.05	6
1-19	31	9.0	6	8	17	3	4	NS	5
20-89	45	13.0	6	19	20	3	9	.01	6
90-199	23	6.7	2	9	12	1	4	.05	3
200+	9	2.6	2	4	3	1	2	NS	1
Bulbar	13	3.8	3	5	5	1	2	NS	1
Bulbo-spinal	64	18.6	2	32	30	1	16	.001	9
Score 0	17	4.9	1	9	7	*	4	.05	2
1-19	19	5.5	-	12	7	-	6	.001	2
20-89	11	3.2	1	5	5	*	2	NS	1
90-199	13	3.8	-	5	8	-	2	.05	2
200+	4	1.2	-	1	3	-	*	NS	1
Fatal	4	1.2	-	4	-	-	2	NS	-
Nonparalytic - Total	62	18.0	18	19	25	9	9	NS	7
Doubtful Poliomyelitis - Total	17	4.9	6	6	5	3	3	NS	1
Not Poliomyelitis - Total	33	9.6	8	11	14	4	5	NS	4

Degree of paralysis in each case determined by muscle examination showing largest score.
* Less than 1 per 100,000.
** See Glossary.
S.L. - Level of statistical significance.
NS - Not significant at level of .05.

Table 15

DEGREE OF PARALYSIS BY DIAGNOSTIC CATEGORY AND VACCINATION STATUS OF STUDY CASES (EXCLUDING ORPHAN VIRUS CASES) OBSERVED AREAS

Degree of Paralysis by Diagnostic Category	Number of Cases					Rate per 100,000			
	Total		Vaccinated	Controls	Other**	Vaccinated	Controls	S.L.	Other**
	Number	Percent							
Study Cases - Total	561	100.0	67	427	67	30	59	.001	50
Poliomyelitis Cases - Total	491	87.5	52	382	57	23	53	.001	43
Paralytic - Total	405	72.2	35	324	46	16	45	.001	34
Spinal	244	43.5	17	197	30	8	27	.001	22
Score 0	78	13.9	10	63	5	5	9	.05	4
1-19	63	11.2	4	50	9	2	7	.01	7
20-89	66	11.8	2	52	12	1	7	.001	9
90-199	26	4.6	1	22	3	*	3	.05	2
200+	10	1.8	-	9	1	-	1	NS	1
Unknown	1	0.2	-	1	-	-	*	NS	-
Bulbar	24	4.3	3	19	2	1	3	NS	1
Bulbo-spinal	125	22.3	15	96	14	7	13	.01	10
Score 0	22	3.9	5	14	3	2	2	NS	2
1-19	38	6.8	6	28	4	3	4	NS	3
20-89	32	5.7	4	25	3	2	3	NS	2
90-199	12	2.1	-	10	2	-	1	NS	1
200+	20	3.6	-	18	2	-	2	.01	1
Unknown	1	0.2	-	1	-	-	*	NS	-
Fatal	12	2.1	-	12	-	-	2	.05	-
Nonparalytic - Total	86	15.3	17	58	11	8	8	NS	8
Doubtful Poliomyelitis - Total	38	6.8	10	22	6	5	3	NS	4
Not Poliomyelitis - Total	32	5.7	5	23	4	2	3	NS	3

Degree of paralysis in each case determined by muscle examination showing largest score.
* Less than 1 per 100,000.
** See Glossary.
S.L. - Level of statistical significance.
NS - Not significant at level of .05.