

WHO/Polio/Int./5 ✓
9 October 1958

ENGLISH ONLY

RESTRICTED

CONFIDENTIAL

23 Oct 1958

EPIDEMIC POLIOMYELITIS AMONG VACCINATED CHILDREN IN ISRAEL ^a

A Report
submitted to The National Foundation

by

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There is no doubt that a severe type 1 poliovirus epidemic occurred among vaccinated children in Israel in 1958. Even if the vaccine was unable to suppress the epidemic, an important question to be answered remains: Was the vaccine able to limit the outbreak to fewer cases than would have otherwise occurred?

Like many other countries,¹ Israel in 1957 obtained epidemiological evidence of the effectiveness of its polio vaccination programme. The following paragraph, written by the Poliomyelitis Advisory Committee² in the spring of 1958, suggested that the reduction in cases of poliomyelitis by over 90 per cent. could be attributed to the two doses of vaccine given to 95 per cent. of the most susceptible group, children six months to three years of age:

"During the winter and spring of 1957 a large-scale immunization programme against poliomyelitis was undertaken in Israel. Salk vaccine, partly imported from the USA and partly produced locally was used for immunization. The programme included,

^a This report includes data through 9 August 1958

For the data in this report, the author is indebted to many people in the Israeli Ministry of Health, particularly to Drs S. Btsh, M. Davis and K. Marberg for epidemiological information, and to Drs N. Goldblum and S. Levine for the laboratory data supplied to him during his visit to Israel. The data of the Israeli epidemiologists and virologists is included in this report with their permission.

in the beginning, infants and children 6 months to 3 years old ("campaign" age group); of the eligible in this age group, 116,000 received two basic inoculations of 0.3 to 0.5 ml of vaccine by the intra- and sub-cutaneous routes, 5500 received one inoculation and 2000 none. Later, infants 4 to 6 months old, children 3 to 4 years old, and children and adults of Anglo-Saxon origin up to the age of 30 years were added to the programme - a total of 22,000 of these received two basic inoculations and several thousands - one inoculation. No vaccine was administered after June 1 1957 until January 1958, when "booster" inoculations were started. In order to evaluate the results of the vaccination, clinical, epidemiological and laboratory data were collected on each case of poliomyelitis which occurred during 1957. A total of 57 cases of poliomyelitis were notified during the whole year. This number of cases compared to a 5-year annual average of 650 cases during the preceding years 1952-56, constitutes a reduction in poliomyelitis incidence of over 90 per cent. Of the 57 cases of poliomyelitis, 7 occurred in January before the effect of immunization could be expected. The remaining 50 cases were distributed as follows: 22 cases in non-immunized infants, less than 1 year old, born during 1957 and, therefore, not included in the vaccination programme; 8 cases occurred in children over 4 years old, and 20 cases in the "campaign" age group. Of these latter 20 cases, 11 had received two inoculations of vaccine, 3 - one inoculation, and 6 none. The immunization seems to have been very effective in reducing the incidence of poliomyelitis in the immunized infants and children. The high effectiveness of the immunization with Salk vaccine may have been due to the fact that almost 95 per cent. of the susceptible age group had received two inoculations of vaccine prior to the poliomyelitis season."

The picture suddenly changed in 1958. In spite of the fact (1) that children who received two inoculations of vaccine in 1957 were given a booster injection in January and February of 1958, and (2) that a large percentage of the children born in 1957 were given two doses of vaccine in 1958, a severe epidemic was well under way in May (see Table 1). The young age-group involved was similar to that previously involved in poliomyelitis epidemics in Israel.³ As shown in Table 2, over 50 per cent. of cases (298 and 527) occurred in children between the ages of six and 23 months.

TABLE 1: COURSE OF 1958 EPIDEMIC (UP TO 9 AUGUST)

Month	Cases by onset
January	5
February	8
March	10
April	8
May	72
June	167
July	194
August (1-9)	58
	Total:
	522

TABLE 2: POLIOMYELITIS IN 1958: CASES BY AGE AND VACCINATION STATUS

Age (yrs)	Total number cases	Number of poliovaccine injections			
		0	1	2	3
0-5/12	36	26	5	5	0
6/12-11/12	124	45	16	63	0
1	174	25	5	108	36
2	82	15	2	3	62
3	39	7	0	3	29
4	22	8	0	2	12
5 and over	46	40	0	3	3
Total	527	166	28	189	142

Isolation and typing of polioviruses

From 1950 (when strains were first isolated and typed in Israel) through 1956, Type I virus has predominated, although both Type II and Type III have also been isolated. In one study, about 60 per cent. of strains were Type I, 20 per cent. Type II, and 20 per cent. Type III. In 1957, during the year of the apparent effectiveness of the vaccine, 45 strains were isolated from paralytic patients. Of these only 10 per cent. belonged to Type I, 40 per cent. to Type II, and 40 per cent. to Type III. In 1958, several hundred strains were isolated from hospitalized patients, and 98 per cent. have proved to be Type I.

Vaccines used

In 1957, the vaccine came from two sources: 70 per cent. from an American manufacturer and 30 per cent. from local production in the Ministry of Health Virus Laboratory. By the guinea-pig antigen-extinction test,¹ the Israeli vaccine and the American vaccine had about the same titre, approximately 1:10 to 1:30.

(At present, vaccines are being produced in Israel in which the second filtration is omitted. Such vaccines have about 30 times the potency of the 1957 vaccines, as measured in guinea-pigs. It should be pointed out that 10 to 20 per cent. of each lot of vaccine is safety tested in Israel. Data on the relative efficiency of the 1957 and late 1958 vaccines in producing antibodies in triply negative children have been obtained by the Ministry of Health Virus Laboratory; these data are discussed later in this report.)

Vaccination Schedule and Antibody Response (see Table 3)During first part of 1957 (prior to June):

First injection: 0.3 ml intracutaneously.

Second injection: 0.5 ml subcutaneously.

After this course, 25 per cent. of some 200 triply negative children responded with Type I antibodies, 90 per cent. with Type II and 40 per cent. with Type III. A positive antibody response refers to a child who had no detectable antibodies against any of the three poliovirus types before vaccination and who responded by a positive test at a serum dilution of 1:8 or higher.

During January-February 1958:

Third injection: 0.5 ml subcutaneously.

About 90 per cent. of children vaccinated in 1957 received the third dose in early 1958. Of 200 children studied serologically, about 100 were still triply negative, or became triply negative again, by the time of the third injection. After the booster dose, 53 per cent. of the 100 responded with Type I antibodies, 90 per cent. with Type II, and 88 per cent with Type III.^a

^a It is important to compare the antibody responses in Israel with those obtained in the United States in triply negative children in 1957. In the United States, one study showed that one month after the second inoculation, 11 to 20 per cent. responded with Type I antibodies, and only after the third inoculation did the number with antibodies increase significantly, that is to 81 to 90 per cent.

TABLE 3. ANTIBODY RESPONSE AFTER VACCINATION OF TRIPLY NEGATIVE CHILDREN*

	Prior to 1957 vaccination	Two weeks after two doses	Prior to third dose in early 1958**	Two weeks after third dose
Type I	0	25%	0	53%
Type II	0	90%	0	90%
Type III	0	40%	0	88%

After the epidemic was well under way, a new lot of vaccine was purchased from the United States and a new Israeli lot of vaccine was given on a mass scale to children regardless of whether or not they had been vaccinated previously. As expected, a number of cases have occurred in recently vaccinated children, but the inoculated limb has not been preferentially selected as the site of paralysis.^a

* Antibodies not detectable in undiluted serum prior to vaccination.

** A selected group of children who either failed to respond after the first two doses or whose antibody level fell below the detectable level by the time the third dose was given.

^a Bacterial vaccines, such as pertussis, are also given in Israel to young children during the poliomyelitis season, with no higher incidence of poliomyelitis, or localization of paralysis, in the inoculated children. It was the current practice in the summer of 1958 to inoculate poliovaccine in one arm and diphtheria vaccine in the other. All vaccines are injected subcutaneously; the more traumatic intramuscular route is avoided.

Attack Rates in Non-vaccinated and Vaccinated Children

Because the cases which were mainly paralytic occurred chiefly in children under the age of five years, the following analysis is concerned with this group at highest risk, namely 223 000 children from six months through four years of age. As shown in Table 4, there was little difference in the rates in the non-vaccinated and those vaccinated twice in 1958. However, the triply-vaccinated group had a rate only one-third that of the non-vaccinated. Even in the triply vaccinated, the rate was high, namely 100 per 100 000.

In order to compare rates in the different groups, it is necessary to consider the ethnic composition of the population involved. The case rate among Arab children in Israel has been, and continues to be, much less than among Jewish children - most likely a reflection of the different levels of sanitation and personal hygiene in the two groups.

The cases in Table 4 refer almost entirely to Jewish children alone. If corrections are made for the low rates among the Arab children in each group, more accurate attack rates for the same age-group (six months to four years) may be calculated for the children in the epidemic.

The social habits of the different groups must be considered in comparing the case rates. About 20 per cent. of the cases in Jewish children were of a mild, transitory nature, and it is unlikely that they would have come to the attention of a physician had the same illness occurred among the Arabs. Thus the true attack rate among the Arabs may be slightly higher than that obtained from the reported cases.

The corrected figures of Table 5 indicate that children vaccinated twice in 1958 had little protection against the epidemic Type I poliovirus, but that the group vaccinated twice in 1957 and boosted in 1958 had only 24 per cent. as many poliomyelitis cases as the non-vaccinated group. However, one must take into account that the group vaccinated three times are older, by at least one year, than the children in the other groups, and that natural immunity in Israel develops rapidly.

Geographic distribution of cases

Even though the first cluster of 1958 cases came from the northern part of the country, Haifa - the city of the north - did not have many cases. On the other hand, Jerusalem - where vaccine was used to the same degree as in Haifa - had a high proportion of cases.

TABLE 4: ANALYSIS OF GROUP AT HIGHEST RISK
223 000 CHILDREN FROM 6 MONTHS TO 4 YEARS (DATA THROUGH 9 AUGUST 1958)

Number of Poliovaccine Injections	Population	Cases	Rate/10 000
0*	40 000	123	31
2	48 000**	179	37
3	135 000	139	10
Totals	223 000	441	20

TABLE 5: ATTACK RATES FOR ARAB AND JEWISH CHILDREN
6 MONTHS TO 4 YEARS OLD

Number of Poliovaccine Injections	Arab children			Jewish children		
	Number	Cases	Rate/10 000	Number	Cases	Rate/10 000
0	18 000	21	12	22 000	102	46
2	6 500	5	8	41 500	174	42
3	10 000	1	1	125 000	138	11
Totals	44 500	27	6	188 500	414	22

Comparison of biennial attack rates

The attack rate of clinical poliomyelitis in Israel for the age-group (six months to four years) considered in this report was 80 per 10 000 at the time of

* Includes a small number of children (3 per cent.) who received only one injection

** This group is made up of children in the most susceptible age group, six to 18 months old, who had not yet lived long enough to receive their third injection. They received their two injections in March and April 1958.

the first large outbreak in 1950 and about 30 per 10 000 each year from 1951 through 1956. Poliomyelitis, particularly Type I, was almost absent in 1957. Thus in comparing the rates in 1958 with those of the period 1950-1956, we must bear in mind that there has been an accumulation of Type I susceptibles for a two-year period. If the rates for an average biennial period between 1950 and 1956 are compared with the rate for 1957-1958, then the two-year rate of about 60 per 10 000 dropped to 20 per 10 000 after the vaccinations were started. These figures again support the view that the vaccine, although unable to prevent clinical disease from occurring, dampened the effect of the epidemic.

Antibody responses to new Israeli vaccines of increased potency

Because of the need for infants to acquire immunity very early in life, efforts are being directed towards developing more potent vaccines. Vaccines used in 1957 and in the early part of 1958 produced antigen-extinction titres in guinea-pigs of about 1:10 - 1:30. To increase their potency, current vaccines are being produced omitting the second filtration. Their antigen-extinction titre in guinea-pigs is over 1:1000. The response of triply-negative children after such vaccine is shown in Tables 6 and 7. The data reveal (a) that after two injections of 1 ml subcutaneously, given three weeks apart, 45 per cent. of 60 children converted to all three types, and (b) that after three injections of 1 ml each, 80 per cent. of the children converted to all three types.

TABLE 6: ANTIBODY TITRES OF 60 TRIPLY-NEGATIVE* INFANTS
FIVE TO SIX MONTHS OLD AT TIME OF VACCINATION

(Schedule: Two injections three weeks apart, with 1 ml each, subcutaneously, of Israeli poliovaccine TRP7-FLO.** Post-vaccination sera obtained two weeks after second injection.)

Antibody titres two weeks after second injection	Type of Antibody		
	I	II	III
Negative at 1:4	17	1	28
Low (1:4 to 1:8)	25	5	8
Medium (1:16 to 1:64)	13	39	18
High (1:128 and over)	5	15	6
Total tested	60	60	60
Percentage positive	72%	98%	53%

TABLE 7: ANTIBODY TITRES OF 55 TRIPLY NEGATIVE* INFANTS
FIVE TO SIX MONTHS OLD AT TIME OF VACCINATION

(Schedule: Three injections on days 0, 7 and 21 with 1 ml each, subcutaneously, of Israeli poliovaccine TRP7-FLO.** Post-vaccination sera obtained two weeks after third injection.)

Antibody titres two weeks after third injection	Type of Antibody		
	I	II	III
Negative at 1:4	6	0	9
Low (1:4 to 1:8)	7	2	9
Medium (1:16 to 1:64)	21	26	26
High (1:128 and over)	21	18	8
Total tested	55	46	52
Percentage positive	89%	100%	83%

* Negative when undiluted serum was used in test

** Antigen-extinction titre in guinea pigs was 1:1000 or greater

DISCUSSION

The children in Israel had been injected with vaccines which produced antibody responses similar to those obtained in the United States in 1957. Yet their level of immunity was insufficient to withstand the challenge of the epidemic strain.

Several questions may be raised as a result of this experience:

1. Have vaccinated children in other parts of the world, including the United States and Denmark, where polio vaccination has been widely practised, had to meet, as yet, the challenge of an epidemic strain? It is noteworthy that in Sweden, where little poliovaccine has been used until 1958, there has been a natural steady drop in cases over the past four years similar to the fall observed in countries practising vaccination.
2. Is the dose of virus higher in exposed young children in subtropical areas such as Israel, so that the level of immunity in vaccinated children was insufficient for protection?
3. Are the viruses which circulated in Israel more neuro-invasive than the strains circulating elsewhere? Similar considerations have been raised each year since 1950, when Israel suffered its first epidemic of poliomyelitis.³
4. If vaccines of higher potency are used so that antibodies are produced in over 90 per cent. of vaccinated children in a period of six to eight weeks, will the level of immunity be raised sufficiently to prevent epidemics?
5. Has an alteration occurred in the antigenic constitution of Type I poliovirus, so that solid protection does not exist in vaccinated persons against all current Type I strains?

CONCLUSIONS

Although Israel practised wide-scale vaccination against poliomyelitis in 1957 and 1958 - with apparent success in 1957 - a severe epidemic in 1958 overrode the immunity attained.

Because the epidemic occurred almost entirely among Jewish children, the figures for this group are the most significant in evaluating the effect of vaccination. In them, the ratio of cases in the triply vaccinated, to those doubly vaccinated, to

those non-vaccinated was 1:3.8:4.2. Thus, even though the case rate among the triply vaccinated group of 125 000 was 11 per 10 000, it was 42 per 10 000 in the children vaccinated twice in 1957, and 46 per 10 000 among the non-vaccinated children.^a This implies a protection rate of 76 per cent. for the triply vaccinated and a negligible 10 per cent. for the doubly vaccinated. However, before the 76 per cent. protection rate can be accepted at face value, one must weigh this against the fact that the children who were doubly vaccinated constituted, because of their young age (six months to 18 months), a more susceptible group than the older children (1-1/2 to four years). Not only had the older children (1-1/2 to four years) lived long enough to have received their three inoculations of vaccine, but many among them probably had developed natural immunity through subclinical infections.

From the available evidence, it appears that if vaccinated children from the United States or elsewhere were subjected to the same virus exposure that the children of Israel had in 1958, severe epidemic poliomyelitis would break out among them. It would appear the better part of wisdom to take steps to increase the levels of polio immunity even in persons already vaccinated, to prevent breaks-through such as occurred in Israel during the epidemic of 1958.

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^a The figures were higher, for all data in this report were only for notified cases through 9 August