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12. VACCINATION WITH ATTENUATED POLIOVIRUSES IN COSTA RICA

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DR. QUIRCE *(presenting the paper)*: On 16 March 1959 Costa Rica embarked upon a nationwide program of vaccination with live attenuated poliovirus vaccine.

A cursory glance at the history of poliomyelitis in Costa Rica in recent years will quickly reveal the reasons for the interest in controlling this disease (Table 1). In 1954 the country suffered one of the most severe epidemics of Type 1 poliomyelitis in medical history. In a population of approximately one million inhabitants there were 1,081 cases of paralytic poliomyelitis. Since that time, the endemic level of the disease has risen steadily with a smaller epidemic occurring again in 1956. A vaccination program with Salk vaccine was carried out in 1956-58, but was gradually diminished when it became clear that the economic resources of the country could not support an adequate campaign with this vaccine.

Toward the end of 1958, therefore, the Ministry of Health requested the advice and support of the Pan American Health Organization in conducting a live poliovirus vaccination program. A plan was adopted to vaccinate all children under 11 years of age in the country, beginning with the metropolitan area of San José, the capital of Costa Rica.

The program is being carried out by giving first the Type 2 virus, followed by Type 1 and Type 3 at approximately one month intervals. Since 10 May, in addition to the Ministry of Health's personnel, the full-time assistance of three epidemiologists has been provided from the PASB, as well as laboratory support from the Middle America Research Unit in Panama, and the PASB Tissue Culture Laboratory at Cali, Colombia. Surveillance of illness possibly related to vaccination is receiving primary attention. In addition, serological surveys are being conducted before and after vaccination, and the antibody responses of newborn infants are being studied.

To 12 June 1959, 80,912 doses of Type 2 and 67,594 doses of Type 1 vaccine have been admin-

TABLE 1. AGE DISTRIBUTION OF REPORTED CASES OF POLIOMYELITIS FOR SELECTED YEARS, COSTA RICA, CENTRAL AMERICA

YEAR	AGE (NUMBER)							
	TOTAL	–1	1–4	5–14	15–24	25–44	45+	UNK.
1941	24	4	18	2	—	—	—	—
1944	84	5	56	23	—	—	—	—
1950–51	37	11	20	6	—	—	—	—
1954	1,081	215	710	106	36	8	1	5
1955	45	4	28	7	5	—	1	—
1956	170	31	112	16	5	4	1	1
1957	51	8	29	8	3	—	1	2
1958	62	14	34	7	1	1	2	3

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istered. Vaccination with Type 3 virus is beginning. Forty vaccinators are employed in a house-to-house program. The vaccine is dispensed in a sweetened cherry-flavored solution by medicine droppers into plastic spoons and fed to the children. The vaccine is accepted readily by the children. The dose is approximately 0.7 cc. of vaccine equivalent to $10^{5.8}$ and $10^{6.2}$ TCD_{50} of Type 2 virus (depending on the lot used) and $10^{6.1}$ TCD_{50} of Type 1 virus.

Vaccination in the metropolitan area of San José will be completed within six weeks, at which time the program will be extended to the rest of the country.

With the poliomyelitis consciousness developed as a result of the 1954 epidemic, the reporting of poliomyelitis and related diseases has improved considerably in Costa Rica. Suspect cases of poliomyelitis are referred to the San Juan de Dios Hospital, which has a large infectious disease section and a modern rehabilitation unit.

Since the onset of the program on 16 March, all cases of suspect poliomyelitis regardless of vaccination status have been investigated, along with all reported reactions to the vaccine. In addition, 202 families in the metropolitan area of San José were surveyed in order to determine unreported polio-like illness.

To date, no definite clinical cases of paralytic poliomyelitis have been detected among vaccinated children. There were two instances of central nervous system illness among vaccinated children, which are under study. One case of transient leg weakness with no other symptoms 30 days following ingestion of Type 2 vaccine has yielded Type 1 poliovirus and possibly another viral agent. The second case had fever and meningismus of 36 hours duration, 5 days after Type 1 vaccination. No viral agents were isolated from throat and rectal swabs inoculated into monkey kidney tissue culture and suckling mice.

Another group of 15 vaccinated children with central nervous system illness has been studied and the diagnosis of paralytic poliomyelitis was ruled out. These include one suspect case of tuberculous meningitis, a cerebellar lesion, an anesthesia complication, isolated weakness of the buccinator muscle, two cases of status epilepticus, two febrile illnesses with convulsions, three bacterial meningitides, and a psoas abscess.

A large number of cases of minor illnesses has been reported by families as possible reactions to the vaccine. These have included febrile respiratory and gastrointestinal complaints which fall into no particular pattern and in the opinion of the investigating team do not differ from illnesses seen among non-vaccinated children. A number of allergic skin reactions has been reported, four of which could be related to vaccination. These are currently being investigated.

In the survey to determine unreported illness 1,101 individuals in 202 families were interviewed. Illness requiring bed rest for longer than 24 hours during the previous month was reported in 62 instances. A physician saw 54 of these cases. There was no instance of paralytic disease. There were two cases of fever and neck pain in one family. These children (both of whom had received 3 doses of Salk vaccine) were not vaccinated with the oral vaccine, but vaccination was carried out in the vicinity of their home.

To date, in the metropolitan area of San José, no cases of paralytic poliomyelitis have been reported in the families of vaccinated children. However, eight cases of suspect poliomyelitis developed among unvaccinated individuals during the vaccination program. These included one case of flaccid paralysis occurring during an attack of mumps, a case of sudden weakness of all extremities with no other symptoms, two cases with fever and neck pain, referred to previously, and four cases in which the prominent symptoms were those of meningitis and spasticity. No viral agents have yet been isolated from available specimens inoculated into monkey kidney and HeLa cell cultures as well as suckling mice.

Among 24 reported suspect poliomyelitis cases in individuals residing outside of the zone of vaccination, four were clinical poliomyelitis, six were possible poliomyelitis, and 14 were cases in which a diagnosis of poliomyelitis was excluded.

Serological Survey of Poliovirus Antibody

In the original program it was planned to collect blood samples from one per cent of the vaccinated population before vaccination and four to six weeks after the last dose. Because of administrative difficulties, only 450 blood specimens were collected from the metropolitan area

TABLE 2. DISTRIBUTION OF POLIOVIRUS ANTIBODY IN SINGLE SPECIMENS AND ALL SPECIMENS BY SEROTYPE AND AGE BEFORE LIVE POLIOVIRUS VACCINATION—SAN JOSÉ, COSTA RICA, 1959

	IN SINGLE SPECIMENS																
CLASSIFICATION OF SINGLE SPECIMENS BY SEROTYPE	AGE IN YEARS																
	6–11 MO.		1		2		3		4		5–9		10–15		ADULT*		TOTAL
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
None	7	78	12	38	7	17	0	0	2	3	1	1	0	0	1	1	30
1, 2, 3	0	0	1	3	6	15	22	43	43	74	156	86	24	89	123	80	375
1, 2	0	0	0	0	4	10	7	14	2	4	7	4	2	7	14	9	36
1, 3	0	0	0	0	0	0	1	2	0	0	6	3	0	0	3	2	10
2, 3	0	0	3	9	12	30	14	27	6	10	8	4	1	4	6	4	50
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
2	0	0	7	22	5	13	4	8	1	2	2	1	0	0	6	4	25
3	2	22	9	28	6	15	3	6	4	7	2	1	0	0	0	0	26
Total	9	100	32	100	40	100	51	100	58	100	182	100	27	100	154	100	553
CLASSIFICATION OF ALL SPECIMENS BY SEROTYPE	IN ALL SPECIMENS																
None	7	78	12	38	7	17	0	0	2	3	1	1	0	0	1	1	30
1, 2, 3	0	0	1	3	6	15	22	43	43	74	156	86	24	89	123	80	375
1	0	0	1	3	10	25	30	49	45	78	169	93	26	96	141	92	422
2	0	0	11	34	27	68	47	92	52	90	173	95	27	100	149	97	486
3	2	22	13	41	24	60	40	78	53	91	172	94	25	93	132	86	461
Number of specimen	9		32		40		51		58		182		27		154		

* Cord blood.

of San José. Of these, approximately one-third had received Salk vaccine. In order to determine whether these specimens were truly representative of the population, a graded random survey was conducted by region. Several readily determined factors relating to the socio-economic status of the 131 families bled and 202 control families were compared. From the preliminary results of this study it became obvious that the test group does not represent a true random sample of the population of San José, because of a predominance of families in the lower socio-economic condition. The data summarizing the distribution of antibodies in the population before vaccination are presented in Table 2.

An additional phase of the program includes the collection of cord blood samples from babies born in hospitals, and the feeding of a combination of Types 2 and 3 vaccine 48 hours after birth. Type 1 virus is being fed one month later. At six months of age the infants will be bled again.

In summary: Costa Rica is engaged in the first nation-wide program in the Americas with the attenuated poliovirus vaccine, aimed at immunizing the population under 11 years of age. The program is approximately two-thirds completed in the metropolitan area of San José. The acceptance of the vaccine on the part of the population has been almost universal. No untoward incident implicating the safety of the vaccine has been encountered. The evaluation of the effectiveness of this program in reducing or eliminating paralytic poliomyelitis will be a problem for the future.

The vaccine strains being used in the program —SM, Type 1; MEF$_1$, Type 2 and Fox, Type 3— were provided by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., through an agreement with PASB.

The serum antibody determinations were carried out by Microbiological Associates, Inc., in Bethesda, Maryland, U.S.A.

DISCUSSION

CHAIRMAN RHODES: The paper presented by Dr. Quirce is open for discussion.

DR. LANGMUIR: I did have the unusual opportunity of being invited by the Pan American Sanitary Bureau as a temporary adviser to accompany Dr. Henderson and Dr. Brody, along with Dr. Shelokov from Panama, on a visit to Costa Rica to discuss the whole problem of the surveillance of this program.

I think everyone is aware that I am deeply concerned about the safety problem.

I suspect that those of us who lived through the fires of the Cutter incident are more sensitive, just as those of us who lived through the depression years, who were hungry, have a little more respect for what can happen in the economic cycle.

I believe deeply that one must have a very fine screen of what goes on, and just the number of reported cases, or even the number of hospital admissions, of paralysis is totally insufficient as an adequate surveillance of one of these problems. We have attenuated strains being fed, and it is quite possible, it seems to me, that patients with relatively minor illnesses, patients with relatively minor degrees of paralysis may follow; and unless there is a thorough and constant search for such cases, they could well be missed.

Such an eventuality might be faced when live virus vaccines are given in other parts of the world, such as in northern Europe, with a largely triple negative population. A series of cases might very well produce another type of Cutter incident.

I was in Costa Rica only four days. There are several others in the room who have been much more active in the continuity of this surveillance program. It is not an easy thing to set up, and I do believe this deserves careful discussion, because a thorough search for cases is essential in any adequate epidemiological evaluation of safety.

DR. DICK: I would like to emphasize what Dr. Langmuir has said, that we are still trying to establish safety and efficacy.

While in many countries a calculated risk may be taken under certain conditions, at the same time I think we must remember that for other countries we have to have evidence, and I appreciate that this is a difficult thing to do. I am saying this now only to indicate that we are still measuring safety and efficacy in other countries.

We have to have the assurance that what is being used will be as safe and as efficient as the Salk vaccination.

One other point that I find difficult to understand is the comparison in the interference which occurs with other enteroviruses, in Dr. Sabin's vaccine, and other enteroviruses, and Dr. Cox' vaccine. I think that is worthy of a certain amount of discussion at this stage.

Finally, I would just like to say that for many years, up to now, cholera vaccination has been used in many parts of the world, used by people who believe that it is effective, and we do not yet know, really, whether it is an effective vaccine. The implications of that are very clear.

DR. COX: These problems of interference which Dr. Dick has raised are quite important. I can only repeat what I said this morning: that when we analyze the data from Andes, Colombia, and that obtained in Minnesota, which perhaps has a population relatively clean of enteroviruses in comparison to Colombia, we have found the immune responses to Types 1 and 3 vaccines to be almost identical. Responses to Type 2 were somewhat lower in Colombia than in Minnesota, but that may have been because in Andes, but not in Minnesota, Type 1 was fed first and it may have interfered with the Type 2 vaccine, since the Type 2 appears to be the least invasive of the three strains with which we are working.

Naturally, we hope to get the answer regarding interference to our strains by other enteroviruses in the Costa Rica trial, and I believe we will.

DR. HENDERSON: Having been involved in the surveillance aspect of the program in Costa Rica, I would like to add that we found it exceptionally difficult to carry out this phase of the

program; that the more active the search for possible cases became, the more difficult it was to know what we were dealing with. Among others, we uncovered a number of limping children and children with stiffness of the neck. We found it a problem to work up each of these cases in complete detail, and yet where should we draw the line?

Even when we had the laboratory data, it was not easy. Dr. Shelokov and I spent considerable time trying to interpret particular isolates and deciding what the interpretation would be if we did or did not get particular antibody responses.

For example, there was an unvaccinated two-year-old near San José who developed paralytic poliomyelitis, and from whom we isolated a Type 2 virus from the stool. We do not know whether this was a wild strain or a vaccine strain. Serology will not help. Since, as Dr. Dick says, "it is not what goes in that is important, it is what comes out," we can only consider this to be a possible vaccine-related case.

A second case was a seven-year-old in San José who was not vaccinated. He developed mumps, followed a week later by flaccid paralysis. At this moment the stool specimens are negative. If we get an antibody response for polio, does this mean he had mumps and polio, or does this indicate incidental intestinal polio infection in an area where the virus has been heavily seeded? I do not know how we can interpret it.

These are but two of the cases we found. There are many more.

In addition to what is listed here in terms of number of cases, I think we saw on the order of 80 to 100 additional individuals, and for us, this relatively small-scale project was a full-time job for one physician and a part-time job for another.

DR. PAUL: An interesting point about this report, already commented upon by two discussants, concerns methods of surveillance. Yesterday, in a brief comment, I expressed the hope that, as we viewed these various field trials and the manner in which they were surveyed, some *approved standards* should be recognized for the assessment of the safety and effectiveness of these vaccines.

There is a point about the enteroviruses which we ought to remember, namely, that some enteroviruses are interferers, as we heard in the paper from Poland this morning; others may not be. We have heard, for instance, from Dr. Fox and his group, as to how ECHO 1, ECHO 9, and, I think, Coxsackie B5 may be incriminated.

We must remember that these interfering infections are not always there. They come in waves, and what is true in 1959 may not be true in 1960.

DR. MONTOYA: I would like to emphasize the difficulties of surveillance, but also to point out that in Costa Rica, fortunately, there are conditions indicating that such a study could be done well. The country is small and has in the capital one large central hospital which receives more patients by plane, from the other states, than any other place in the world. Also, it has a fairly adequate number of physicians giving a rather complete medical coverage to the population. For those reasons I believe that although it is a full-time job, and quite a difficult one, Costa Rica offers good opportunities for successful work.

DR. PAYNE: In considering the question of safety, there is one factor which has not, I believe, been mentioned at all, and that is the problem of provocation poliomyelitis. One of WHO's field teams had an unfortunate experience in Western Samoa, in which repository penicillin was being used in a yaws control program.

There was an epidemic of poliomyelitis comprising 25 cases, of which 24 cases were pure provocation poliomyelitis. In each case the paralysis was either confined to or began in the injected limb.

If this campaign had not been going on, there would have been presumably just one case of poliomyelitis due to the prevalent strain, which was apparently not highly paralytogenic.

I believe that if we are feeding live virus, we have to bear the possibility in mind that some form of provocation might make these viruses more likely to cause symptoms.

DR. MONTOYA: I would like to clarify the remarks made by Dr. Henderson regarding the difficulties of surveillance encountered in San José. It is important to become acquainted with the morbidity picture in the country at this time

of the year—with epidemics of measles and mumps going on—in order to be able to exclude many apparent associations with the vaccine. I am sure that if one were to carry out a surveillance program for some other problem in other parts of the country at this time, or even in San José after the vaccination program has been completed, one would encounter the same findings, if not worse. So, we must take into account what is going on currently in the country, and not necessarily relate the findings from a single sampling to the vaccine.