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Vaccination with the CHAT Strain of Type 1 Attenuated Poliomyelitis Virus in Léopoldville, Congo*

3. Safety and Efficacy during the First 21 Months of Study

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Between August 1958 and April 1960 nearly all children less than five years old in Léopoldville were orally vaccinated with the CHAT, type 1, attenuated poliovirus strain of Koprowski. In a previous report, the first nine months of the campaign were reviewed and tentative conclusions were drawn concerning the safety and efficacy of the vaccine. The present paper is a report on a further twelve-month period of observation. Additional epidemiological data and virological studies, including the use of virus markers for assessing the safety of the attenuated strain, lend added support to the earlier conclusions. Of particular interest were the results of virus isolations from patients with paralytic poliomyelitis, there being an apparent shift in the predominant causative agent from type 1 to type 3 poliovirus concomitant with the completion of the type 1 vaccination campaign.

Vaccination with the CHAT type 1 strain (Koprowski, 1957) of attenuated poliovirus in Léopoldville, Republic of the Congo (fomerly Belgian Congo), started in August 1958. By April 1960, about 21 months after the commencement of the campaign, approximately 75 000 African children under the age of 5 years had been vaccinated. This represents an increase of roughly 30 000 over the total number of vaccinees already reported. Details of organization of the trial and the selection of susceptibles, and observations on safety and efficacy up to 30 April 1959 were given in earlier reports (Lebrun et al., 1960; Plotkin et al., 1960; Gard, 1960; Koprowski et al., 1960). This communication is concerned with a year's further studies.

Table 1 summarizes the vaccination and population statistics for Congolese children of the age-group in which almost all poliomyelitis cases occur, that is, 6 months through 2 years. By 30 April 1960, 41 400 of approximately 46 200 children in this most susceptible age-group had been fed CHAT virus.

TABLE 1

POPULATION AND VACCINATION STATISTICS FOR LÉOPOLDVILLE AFRICAN CHILDREN AGED 6 MONTHS TO 2 YEARS

Area of city	Average population (in thousands)		Vaccinees (in thousands)	
	1958	1959	30 April 1959	30 April 1960
Ancienne Cité	13.5	14.7	10.7	13.6
Nouvelle Cité	15.1	15.6	7.0	12.4
" Five districts "	12.0	15.9	7.9	15.4
Total	40.6	46.2	25.6	41.4

POLIOMYELITIS INCIDENCE JANUARY 1958 THROUGH APRIL 1960

The monthly incidence of paralytic poliomyelitis during 1958, 1959 and the first four months of 1960 is given in Table 2. A type 1 epidemic occurred during the latter part of 1958 and early 1959, ending in March 1959. Beginning in May 1959 and continuing into 1960, there were from 3 to 10 cases of paralytic poliomyelitis each month, without a sharp epidemic peak.

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TABLE 2

REPORTED CASES OF PARALYTIC POLIOMYELITIS BY MONTH AND BY VACCINATION STATUS,[a] JANUARY 1958 THROUGH APRIL 1960

Year	Reported cases each month (vaccinated cases in parentheses)											
	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1958	12	5	6	1	2	0	1	0 (—)	1 (—)	3 (—)	9 (1)	37 (—)
1959	24 (3)	15 (2)	9 (4)	1 (—)	5 (1)	6 (1)	10 (4)	9 (5)	7 (3)	8 (4)	6 (3)	6 (3)
1960	4 (1)	6 (3)	6 (1)	3 (—)								

[a] Vaccination began in August 1958.

The age distribution of recent cases is compared in Table 3 with the age distribution of the 1958-59 epidemic, to which it is similar.

For the purposes of analysis, Léopoldville can be divided into three major geographical areas—the Ancienne Cité, the Nouvelle Cité, and five smaller districts (Ndjili, Matete, Kintambo, Bandalungwa, and Camp Léopoldville). Table 4 gives the number of cases in each area during the year under consideration and divides the patients into two groups, that which had been given no vaccine and that to which CHAT virus had been administered before the onset of illness. Of 76 cases, 47 were in non-vaccinated infants and 29 in vaccinated infants. It is of interest to note that in the Ancienne Cité, the number of vaccinated cases exceeded the number of non-vaccinated cases, whereas the opposite was true in the other two districts (see Discussion).

Virological studies have been done on poliomyelitis cases since the beginning of the vaccination campaign. Table 5 summarizes the monthly experience in isolation of viruses from cases of paralytic poliomyelitis. During the 1958-59 epidemic almost all isolated viruses were of type 1, with an occasional type 2 or 3. Beginning in July 1959, a change occurred: type 3 poliovirus was isolated more frequently. Virological data through February 1960 are summarized in Table 6, which shows the identity of the virus and the residential area and vaccination status of the individual from whom it was isolated. From June 1959 through February 1960, 16 isolations of type 3 were made, as well as 5 of type 1, 5 of type 2, and 6 of non-poliomyelitis viruses. From vaccinated individuals, 14 viruses were isolated of which 9 were of type 3. Eighteen viruses were isolated from non-vaccinated individuals, of which 7 were of type 3.

TABLE 3

AGE DISTRIBUTION OF PARALYTIC POLIOMYELITIS IN LÉOPOLDVILLE AFRICAN CHILDREN SINCE BEGINNING OF VACCINATION

Age-group	Aug. 1958-April 1959		May 1959-April 1960	
	No.	%	No.	%
<6 months	—	—	3	4
6-11 months	25	25	14	18
1 year	57	58	37	49
2 years	15	15	16	21
3 years	1	1	4	5
4 years and over	1	1	2	3
Total	99	100	76	100

TABLE 4

PARALYTIC POLIOMYELITIS IN AFRICAN CHILDREN BY AREA OF LÉOPOLDVILLE AND VACCINATION STATUS, MAY 1959-APRIL 1960

Area	Cases		
	Vaccinated	Non-Vaccinated	Total
Ancienne Cité	14	7	21
Nouvelle Cité	10	21	31
" Five districts "	5	19	24
Total	29	47	76

SAFETY

In order to evaluate the significance of the Léopoldville vaccination campaign with regard to evidence of safety, it is necessary to estimate the numbers of vaccinees infected with attenuated virus who were actually susceptible to poliomyelitis. Table 7 provides such an estimate.

The number of children vaccinated in each age-group combined with the percentages of seronegativity found in the pre-vaccination survey gives a computation of 35 300 type 1 negative and 18 400 triple negatives vaccinated. It has been previously determined (Plotkin et al., 1960) that up to 37% of vaccinees may have been infected by the epidemic, and that 40% of vaccinees were probably not vaccinated successfully. After subtraction of the 37% who were probably infected by the type 1 epidemic, there remain 24 300 type 1 negatives and 12 800 triple negatives. Of these numbers, 14 600 and 7700 were probably infected with attenuated virus.

Since the beginning of the vaccination campaign, 39 cases of paralytic poliomyelitis have occurred in vaccinated individuals. The intervals between vaccination and illness are given in Table 8: only 5 of the 39 illnesses had onsets within a period of 2 months from the time of vaccination. If one multiplies the number of vaccinations given each month by the incidence of poliomyelitis during that month, an expected number of 7.8 cases of poliomyelitis in vaccinees of less than 60 days is obtained, which is more than the 5 cases that actually occurred.

The five cases with onsets less than 2 months after vaccination are further analysed in Table 9. The first two cases had incubation periods shorter than one week, and the acid agar, MS, temperature, and serological characteristics of the isolated viruses did not resemble those of CHAT. Similar laboratory observations on the virus isolated from the third

TABLE 5

VIRUS ISOLATIONS FROM STOOLS IN PARALYTIC CASES, AUGUST 1958-DECEMBER 1959

Month	Poliovirus type 1	Poliovirus type 2	Poliovirus type 3	Non-poliovirus
1958 Aug.	—	—	—	—
Sept.	—	—	—	—
Oct.	1	—	—	—
Nov.	1	—	—	—
Dec.	6	—	1	2
1959 Jan.	6	—	1	—
Feb.	5	1	—	—
March	2	—	—	—
April	—	1	—	—
May	—	—	—	—
June	2	1	1	1
July	2	1	2	1
Aug.	1	—	1	—
Sept.	—	—	6	—
Oct.	—	—	2	2
Nov.	—	—	—	1
Dec.	—	—	2	—
1960 Jan.	—	—	1	1
Feb.	—	3	1	—

TABLE 6

VIRUS ISOLATIONS FROM STOOLS IN PARALYTIC CASES ANALYSED BY LOCATION OF CASE AND VACCINATION STATUS, JUNE 1959-FEBRUARY 1960

Area	Group	Virus isolation				
		Poliovirus type 1	Poliovirus type 2	Poliovirus type 3	Non-poliovirus	Total
Ancienne Cité	Total	—	3	6	1	10
Nouvelle Cité	Total	2	2	3	3	10
" Five districts "	Total	3	—	7	2	13
All	Vaccinated	1	2	9	2	14
	Non-vaccinated	4	3	7	4	18
	Total	5	5	16	6	32

TABLE 7
PROBABLE NUMBERS OF HOMOTYPIC SERONEGATIVES AND TRIPLE SERONEGATIVES VACCINATED WITH CHAT VIRUS

Age-group	Number vaccinated (thousands)	Type 1 negative [a] (%)	Triple negative [a] (%)	Type 1 negatives vaccinated (thousands)	Triple negatives vaccinated (thousands)
<1 year	21.0	—	—	—	—
<6 months	10.7	—	—	—	—
6-11 months	10.3	91	74	9.4	7.6
1 year	15.2	77	46	11.7	7.0
2 years	15.9	54	18	8.6	2.9
3 years	13.5	33	7	4.5	0.9
4 years and over	10.8	10	0	1.1	—
Total	76.4			35.3	18.4
Minus 37 % infected during epidemic [b]				24.3	12.8
Minus 40 % not infected by vaccine [b]				14.8	7.7

[a] Based on results of pre-vaccination serological survey given in Table 4 of Plotkin et al. (1960).
[b] Based on results of post-vaccination serological survey given in Table 5 of Plotkin et al. (1960).

case implied that it was not a descendant of the CHAT strain.

The fourth case did not develop complement-fixing antibodies to poliomyelitis after the onset of paralysis, although neutralizing antibodies to all three types of poliomyelitis were present. Unfortunately, a stool specimen was not obtained. From the last case, a type 3 virus was isolated.

It should be stated that no attenuated type 3 vaccine was used in Léopoldville until vaccination of the European population was begun in September 1959, well after the beginning and the peak of the natural type 3 epidemic, which as is seen in Table 5, was reported in September 1959; the cases therefore had been infected several weeks earlier.

TABLE 8
INTERVAL BETWEEN VACCINATION AND ILLNESS IN VACCINATED CASES

Interval (months)	No. of cases
<1	5 [a]
1-	—
2-	5
3-5	13
6-8	10
9-11	6

[a] Expected number = 7.8.

All type 1 polioviruses isolated in Léopoldville from paralytic cases, both vaccinated and non-vaccinated, have been studied in at least two laboratory tests: first, for reproductive capacity at 40°C (Lwoff & Lwoff, 1959); and second, for ability to form plaques under a specific anti-CHAT serum (Wecker, 1960).

Table 10 shows the results of these tests applied to known human intestinal passages of the CHAT virus. To date, none of the viruses tested, including up to three human intestinal passages, has differed from CHAT with respect to the temperature character or to what might be called its antigenic character. On the other hand, similar tests of 10 type 1 viruses isolated from patients in Léopoldville before April 1959, the results of which have already been reported (Koprowski et al., 1960; Plotkin et al., 1960), showed characters opposite to those of CHAT.

Tests of type 1 viruses isolated more recently in Léopoldville are shown in Table 11. Viruses 211 and 212 were isolated from vaccinated infants, and resembled CHAT in their temperature and serological characters. Isolations from non-vaccinated

TABLE 9
SUMMARY OF CASES HAVING ONSET OF POLIOMYELITIS WITHIN A MONTH OF VACCINATION

Patient No.	Date of vaccination (1959)	Date of onset of illness (1959)	Interval from vaccination to onset (days)	Faecal poliovirus type	CF test		
					Poliovirus type 1	2	3
63	9 or 10 Jan.	11 Jan.	1-2	1			
81	2 Feb.	8(?) Feb.	6 or less	1			
93	6 Feb.	26 Feb.	20	1	+	0	0
201	15 April	30 April	15	NT	0	0	0
46-59	20 Oct.	18 Nov.	29	3			

NT = not tested.

children are represented by viruses 233, 235, 224 and 229; virus 220 was isolated from a vaccinated paralytic child. All of these viruses were able to grow at 40°C and were capable of breaking through the CHAT antiserum.

Of particular interest is virus 525, isolated from a 32-year old European woman who developed poliomyelitis one month after coming to a village in the Congo. In this village and in neighbouring villages during the latter part of 1959 there had been several

TABLE 10
GENETIC AND SEROLOGICAL MARKERS OF CHAT VIRUS AND ITS HUMAN PASSAGE STRAINS

Strain	Human intestinal passage	Markers [a]				
		Temperature	MS	Neutralized by anti-CHAT serum	IC Par.	Pathogenic lesions
CHAT	—	Cold	MS	Yes	0/5	0/5
C-1	1	Cold	MS	Yes		
D-1	↓	Cold	MS	Yes		
I-1		Cold	MS	NT		
L-1		Cold	MS	Yes		
R-1		Cold	MS	NT		
Q-1	↓	Cold	MS	Yes	0/4	0/4
O-5	2	Intermediary	MS	Yes		
Q-5	2	Cold	MS	Yes	0/3	1/3
Q-2	3	Cold	MS	Yes	0/7	0/7
Mahoney	—	Ho	MS+	No		
Virulent	?	Hot(6)	MS+(10)	No(6)		
10 " wild " [b]		Intermediary (1) NT(3)		NT(4)		

[a] Hot = grows equally well in tissue culture at 40°C and at 37°C; Intermediary = grows at 40°C and at 37°C, but with a much higher titre at 37°C; Cold = grows poorly at 40°C; MS+ = forms plaques as well in monkey kidney stable line culture as in primary monkey kidney; MS = plaque formation inhibited in established monkey kidney culture; IC Par. = Paralysis in monkeys after intracerebral inoculation of virus; NT = not tested.

[b] Ten " wild " strains isolated from paralytic patients during an epidemic.

TABLE 11

CHARACTERISTICS OF TYPE 1 POLIOVIRUSES ISOLATED IN LÉOPOLDVILLE

Virus	Group	Log $TCID_{50}$ at 37°C minus Log $TCID_{50}$ at 40°C	Control plaque diameter under CHAT antiserum (%)
CHAT	Vaccine	>6.0	0
Mahoney	Virulent control	0.0	40
211	Vaccinated children	>2.7	10
212		>4.5	0
233	Non-vaccinated paralytic cases	0.5	50
235		0.2	45
224		0.8	40
229		0.0	50
220	Vaccinated paralytic case	0.3	38
525	Non-vaccinated paralytic case in vaccinated community	0.0	43

cases of type 1 paralytic poliomyelitis. Consequently, on 30 November 1959, CHAT was administered to 374 Europeans of all ages and 253 African children less than 5 years old. How many remained unvaccinated in the village is unknown, but there is no doubt that there were many Africans who failed to appear for vaccination. On 10 January 1960, one month after her arrival and 41 days after the vaccination had been performed in the village, the European woman developed bulbospinal poliomyelitis. A type 1 poliovirus was isolated from her stool which is shown in Table 11 to be capable of easily breaking through the CHAT antiserum. This woman has two young children, and it is certainly conceivable that they transmitted a wild type 1 poliovirus to her.

EFFICACY OF VACCINATION

In the first report of the vaccination campaign in Léopoldville (Plotkin et al., 1960), an attempt was made to calculate the efficacy of vaccination despite numerous problems in the evaluation of the results. Using two methods, it was determined that there was at least mathematical evidence that the vaccine afforded approximately 60% protection. It was also shown that the antibody response to vaccination was only 60%, presumably because of enterovirus

TABLE 12

ESTIMATED PROTECTION BY CHAT VIRUS AGAINST PARALYTIC POLIOMYELITIS IN LÉOPOLDVILLE AFRICAN CHILDREN AGED 6 MONTHS THROUGH 2 YEARS

District	Period [a]	Group	Cases	Person-weeks	Rate per 10^5 person-weeks	Estimated protection (%)
Ancienne Cité	1	Vaccinated	4	64 800	6.2	53
		Non-vaccinated	27	205 200	13.2	
	2	Vaccinated	13	774 800	1.7	52
		Non-vaccinated	5	142 480	3.5	
Nouvelle Cité	1	Vaccinated	2	47 800	4.2	71
		Non-vaccinated	41	284 200	14.4	
	2	Vaccinated	8	677 560	1.2	80
		Non-vaccinated	18	295 880	6.1	
" Five districts "	1	Vaccinated	4	130 400	3.0	68
		Non-vaccinated	13	133 600	9.7	
	2	Vaccinated	5	686 920	0.7	88
		Non-vaccinated	18	305 240	5.9	
All [b]		Vaccinated	34		2.6 [c]	67
		Non-vaccinated	81		7.7 [c]	

[a] 1 = Period of type 1 epidemic, October 1958 through March 1959.
2 = End of April 1959 through April 1960.

[b] Excluding period 1 in Nouvelle Cité.

[c] Average of rates given above, excluding period 1 in Nouvelle Cité.

TABLE 13
SIGNIFICANCE OF ESTIMATED PROTECTIVE EFFECT OF CHAT VACCINE AGAINST POLIOMYELITIS IN VACCINATED LÉOPOLDVILLE AFRICAN CHILDREN AGED 6 MONTHS THROUGH 2 YEARS

District	Cases observed	Cases expected	χ^2
Ancienne Cité	17	23.73	1.91
Nouvelle Cité	10	20.89	5.67
" Five districts "	9	24.93	10.28
All	36	69.55	17.86 [a]

[a] N = 2; P < 0.01.

interference. Another year's data have been incorporated into calculations which are presented in two tables.

Table 12 shows calculation of efficacy by the person-week method. Two time periods were taken: first, October 1958 through March 1959 (the type 1 epidemic) and second, May 1959 through April 1960 (the recent experience). For each time period, those vaccinated at the beginning of the period were multiplied by the total number of weeks, and those vaccinated later were multiplied by the number of weeks remaining to the end of the period. The cumulative experience of the vaccinated and unvaccinated populations was thus determined. Over all, an average rate of 7.7 cases per 100 000 person-weeks was observed for the unvaccinated population, in contrast to 2.6 cases per 100 000 person-weeks in the vaccinated. From these figures the estimated protection was 67%.

In the second method of calculation, the expected number of cases in vaccinated subjects was computed by multiplying the number of cases during a given week by the cumulative number vaccinated as of two weeks before, and dividing the result by the total number of vaccinated and non-vaccinated individuals. Although 69.55 cases would have been expected in vaccinated individuals, only 36 actually occurred (Table 13). χ^2 was highly significant with a probability of less than 0.01.

DISCUSSION

The apparent shift from type 1 to type 3 as the predominant causative agent of paralytic poliomyelitis in Léopoldville is the most interesting fact reported here. Unfortunately, it is open to at least three interpretations. It is possible that chance alone was responsible for the exclusive isolation of type 3 from Léopoldville for a period of at least six months. However, in view of the high endemicity of polioviruses of all three types demonstrated by Vandeputte (1960) over a period of twelve months in Léopoldville, it is difficult to accept chance as the sole cause of the change.

Another explanation might be that the 1958-59 epidemic exhausted type 1 susceptibles. This interpretation can probably be discarded on two grounds: first, that post-epidemic blood specimens suggest only a 37% reduction of susceptibles during the epidemic; and, second, that about 30 000 infants unborn or less than 6 months old at the end of the 1958-59 epidemic entered the susceptible group after the epidemic.

The third explanation might be that widespread vaccination with type 1 attenuated virus cut down the circulation of wild type 1 virus by converting intestinal tracts susceptible to multiplication of type 1 poliovirus into immune intestinal tracts.

Probably, all three factors mentioned operated to reduce type 1 paralytic poliomyelitis. Only a longer observation period would permit a conclusion as to the relative importance of vaccination in this situation. It is unfortunate that the political situation has made it impossible to continue these observations.

The Léopoldville vaccination trial demonstrates the large number of vaccinations necessary in order to accumulate smaller numbers of probably infected susceptibles—the prime test of safety. About 14 600 type 1 negatives, of whom 7700 were triple negative, were probably infected with CHAT given to over 75 000 children. It was shown that five cases of paralytic poliomyelitis occurred within two months of vaccination with CHAT, a figure less than expected from chance. In no case did the epidemiological or laboratory findings suggest a causal association between the vaccine and the illness. The same could be said with respect to non-vaccinated cases, in so far as the laboratory identification of the causative strains was concerned.

Incorporation of the recent data into calculations of the efficacy of vaccination gave results similar to those reported previously (Plotkin et al., 1960). The probability that the apparent protective effect of the vaccine is a real one has now reached 99%.

It may be objected that the evidence of protection should not be quite so good considering that many

recent cases apparently were caused by type 3 virus. In this regard it is of interest that in the Ancienne Cité, where no type 1 viruses were isolated during the type 3 epidemic, there was the poorest evidence of protection, whereas the apparent protection was higher in the other two areas, in which type 1 virus was isolated during June, July and August 1959. In other words, the areas which showed the highest levels of protection were those in which type 1 virus was circulating at times during this period. It is also possible, of course, that type 1 immunity partially protects against type 3 poliomyelitis.

Finally, the high rate of paralytic poliomyelitis in this tropical setting should be noted. For the twelve-month periods May 1958 through April 1959 and May 1959 through April 1960 the rates were 29.5 and 21.5 per 100 000 respectively. These rates of paralytic poliomyelitis are higher than those recorded in the United States of America in pre-Salk vaccination years. Inasmuch as most cases in Léopoldville are in infants, it appears that there is a high ratio of apparent to inapparent poliovirus infection in infants in this and possibly in other African communities.

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RÉSUMÉ

A partir d'août 1958, 75 000 enfants africains de Léopoldville, âgés de moins de 5 ans, ont été vaccinés contre la poliomyélite au moyen du vaccin CHAT de type 1. Environ 46 000 de ces enfants appartenaient au groupe d'âge le plus vulnérable — 0-3 ans; au 30 avril 1960, 41 000 de ceux-ci avaient été vaccinés.

Durant cette période de 21 mois, il y eut une épidémie de poliomyélite paralytique de type 1, suivie d'une brève poussée de type 3.

Au cours des 6 derniers mois d'observation, aucun virus de type 1 n'a été isolé de malades frappés de formes paralytiques. Au cours de la période suivant immédiatement la vaccination, la fréquence des cas ne fut pas plus élevée parmi les vaccinés que l'on ne pouvait s'y attendre dans un groupe pris au hasard.

Les virus de type 1 isolés de sujets vaccinés et non vaccinés différaient par un ou deux de leurs caractères du virus CHAT et de ses formes connues de passage sur l'homme.

L'efficacité de la vaccination fut évaluée à 67%. C'est dans les secteurs de la ville où la poliomyélite était exclusivement de type 3 que la différence fut la plus faible entre la fréquence des cas, supputée et observée, chez les vaccinés.

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