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Oral poliovirus vaccine in tropical Africa: greater impact on incidence of paralytic disease than expected from coverage surveys and seroconversion rates*

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During the first 5 years of a poliomyelitis control programme in Yaounde, Cameroon, a maximum of 35% of children aged 12–23 months were estimated to have received three doses of trivalent oral vaccine. Despite this low immunization coverage and low seroconversion rates, which were determined concurrently, the estimated incidence of paralytic poliomyelitis decreased by 85%.

A detailed study of immunized children and of children living in the same households suggests that community spread of the vaccine virus and cross-immunity may have partly been responsible for the dramatic decrease in the incidence of paralytic disease, and that competing non-polio enterovirus infection was not a cause for the low seroconversion rates. These results suggest that immunization coverage and seroconversion rates alone are not sufficient criteria for determining the effectiveness of control programmes that use oral poliovirus vaccine in tropical Africa; surveillance of the incidence of paralytic disease must also be carried out.

The annual incidence of paralytic poliomyelitis in tropical West Africa, as estimated by lameness surveys of children 5–11 years of age, ranges from 28 to 53 per 100 000 general population, which makes this disease a significant public health problem (*1*).[a] Seroconversion studies in at least two West African countries suggest poor antibody response to oral poliovirus vaccine. In Nigeria in the early 1970s, the maximum seroconversion rate after three doses of oral vaccine given at 30-day intervals was 88% for type 2 virus, but less than 50% for both types 1 and 3 (*2*). In Ghana in the same period, seroconversion rates to each of the three virus types after two doses of vaccine were less than 50%, and 23% of the children remained negative to all three types (*3*). Because these seroconversion rates after oral vaccine were significantly lower than those after inactivated poliovirus vaccine and after oral vaccine in temperate climates, the investigators in these studies recommended further study of oral poliovirus vaccine in tropical countries, and the use of inactivated vaccine in Nigeria.

In 1975, a poliomyelitis control programme was begun in and around Yaounde, the capital of Cameroon, and following the recommendation of WHO's Expanded Programme on Immunization (EPI), the Ministry of Health chose trivalent oral poliovirus vaccine (TOPV). The vaccine was available every day at fixed health centres for children 2–24 months of age. In accordance with WHO recommendations, three doses of vaccine were given with a minimum interval of one month between doses

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[a] BERNIER, R. H. *Prevalence survey technique for paralytic polio: an update*. Unpublished WHO document, EPI/GAG/83, 1983.

to complete the primary immunization. A booster dose was offered to children 12 months later.

The climate of Yaounde is tropical, with a mean daily temperature of 25 °C, ranging from 15 °C in the rainy season to 33 °C at the end of the dry season. The population of Yaounde in 1976 was estimated at 314 000, with a birth rate of 38 per 1000, and 17% of the population were under the age of 5 years. Before this programme started in 1975, inactivated poliovirus vaccine had been administered sporadically in Yaounde by private physicians, but no regular immunizations against poliomyelitis were offered at the city's government health facilities. This report describes disease surveillance and programme monitoring activities conducted in Yaounde as part of the poliomyelitis control programme between 1975 and 1980.

METHODS

Estimation of the annual incidence of paralytic poliomyelitis

Registers at the Yaounde Centre for Treatment and Re-education of Handicapped Children were reviewed each year from 1974 to 1980. The name, sex, and date of onset of paralysis were recorded for each child who had been examined and given the diagnosis of poliomyelitis and/or flaccid paralysis. Only those children whose parents gave Yaounde as the place of residence at the time of onset of paralysis were included in the study.

From this information, the number of cases of paralytic poliomyelitis by year and by age of onset were tabulated. The annual incidence of paralytic poliomyelitis per 100 000 general population was estimated using the number of cases registered per year and the population projections for Yaounde based on the 1969 and 1976 census.

Estimation of immunization coverage

Surveys of immunization coverage of randomly selected children were conducted in Yaounde in 1976, 1977, and 1979 in order to assess the degree of acceptance of the vaccine by the community. Children 12–23 months of age were chosen for the surveys by a two-stage cluster sampling method (*4*). The total number of doses of poliovirus vaccine received by each child surveyed was recorded either directly from the child's vaccination card or from the immunization history as related by a parent. The population coverage was calculated by dividing the number of children immunized by the total number of children surveyed. Only children who had lived in Yaounde during the three-month period preceding the survey were considered in the final estimation of immunization coverage.

Estimation of the antibody response to TOPV

During the period May–August 1979, three doses of TOPV were administered to children 2–11 months of age. The vaccine was transported to the health centre on wet ice and the dose recommended by the manufacturer was administered orally. Only the first dose of vaccine was administered at the immunization centre, after which the children were accompanied home by the vaccinator and a laboratory technician. The same team administered the second and third doses of vaccine (at 30-day intervals) to the children in their homes. Capillary blood for antibody determination was obtained by fingerprick and collected in 100-μl capillary tubes or on filter-paper as described by Mathews (*5*). Serum specimens were tested for neutralizing antibodies to polioviruses 1, 2, and 3 by incubating the virus with the sera or filter-paper eluate, then inoculating the virus onto primary monkey (*Macacus cynomolgus*) kidney cell cultures and observing whether there was neutralization of the cytopathic effect (CPE). All sera were titrated for neutralizing antibody to each of the three types of poliovirus in serial dilutions from 1:10 to 1:640. Any serum with a titre less than 1:10 was considered antibody-negative. A fourfold or greater increase in antibody from a starting titre of less than 1:10 was considered as evidence of seroconversion to the vaccine. The polio-antibody status of children prior to immunization was tabulated for children vaccinated; the antibody status at 30 days after the first and second doses of vaccine was tabulated only for those children who were antibody-negative to all three virus types at the start of the study. One unopened vial of vaccine which had been transported to the field during each 30-day interval between immunizations was refrozen and stored at −20 °C; the virus titre of this vaccine was determined upon completion of the study by standard virus titration techniques. All seroconversion studies were conducted in and around Yaounde during the period of low poliovirus transmission.

Enterovirus infection among immunized children

Immediately prior to administration of the first, second, and third doses of vaccine, rectal swabs for virus isolation were obtained from each child. The swabs were placed in sterile vials containing Hank's solution, which were transported on wet ice and stored frozen at −20 °C until analysis. Enterovirus was identified by inoculation of this solution, after thawing, onto a culture of primary monkey kidney

cells. Those specimens producing CPE were further identified by incubation with known antisera to polio and non-polio-enterovirus (intersecting pools according to Melnick), then reinoculated onto primary monkey cell cultures to observe for neutralization of CPE. All specimens that failed to produce CPE in monkey kidney cells were then inoculated onto a continuous line of baby green monkey (BGM) cells. Poliovirus of vaccine origin was identified by the test for reproductive capacity at supraoptimal temperatures (RCT test) (*6*). Vaccine and wild strains of virus were further differentiated by neutralization of specific monoclonal antibodies (Sabin types 1, 2, and 3 and Mahoney type 1, MEF-1 type 2, and Saukett type 3) prepared at the Institut Pasteur (Paris) as described by Crainic et al. (*7*).

Poliovirus and non-polio-enterovirus infection rates were calculated among those children who were negative to all three antibodies at the start of the study. Non-polio-enterovirus infection rates were calculated among those who had an antibody response 30 days later and compared with those who did not have an antibody response. Poliovirus infection rates were also calculated for this same triple-antibody-negative group of children prior to the first dose of vaccine, and 30 days after the first and second doses of vaccine.

Enterovirus infection rates among household contacts of immunized children

Rectal swabs were collected from older siblings or other children under five years of age who lived in the same household as the immunized children. Specimens were collected at 30-day intervals, stored and analysed as described previously. Poliovirus and non-polio-enterovirus infection rates were calculated among this household contact group prior to immunization of siblings and 30 days after the first and second doses of vaccine had been given.

RESULTS

Annual incidence of paralytic poliomyelitis and immunization coverage

The estimated annual incidence of paralytic poliomyelitis occurring in Yaounde steadily decreased from 66 per 100 000 general population with onset in 1975 to 10 per 100 000 with onset in 1979 (Table 1), which represents an 85% reduction. Among children with paralytic poliomyelitis, 78% were less than 24 months of age at the onset of paralysis.

Immunization coverage in Yaounde, as was estimated annually by sample surveys of children 12–23 months of age, is shown in Table 1. By August 1979, 45% of 221 children surveyed had received at least two doses of TOPV, and 35% had received three doses.

Seroconversion to the vaccine used in the programme

A total of 91 children 2–11 months of age were included in the seroconversion study. On enrolment, 61 (67%) of these children were triple-antibody negative (antibody titre less than 1:10) and 4 (4%) had neutralizing antibody to all three types of poliovirus (Table 2). The mean age of the triple-antibody-negative children was 4.6 months with a range of 3–11 months. Among the 33 children followed up for

Table 1. Paralytic poliomyelitis by year of onset, based on records from the Centre for Treatment and Re-education of Handicapped Children, and immunization coverage in Yaounde, Cameroon, 1974–80

Year of onset	Total with diagnosis of paralytic poliomyelitis	Estimated population in Yaounde	Estimated annual incidence (per 100 000)	Percentage of children aged 12–23 months who received TOPV	
				Two doses	Three doses
1974	154	255 116	60	–	–
1975	184	278 076	66	–	–
1976	96	313 706	31	22	17
1977	63	341 939	18	36	27
1978	71	372 714	19	33	27
1979	39	406 258	10	45	35
1980	42	442 821	9	–	–

Table 2. Antibody status of 2-11-month-old children at the start of the seroconversion study, and after one and two doses of TOPV, Yaounde, Cameroon, 1978

	No. of children examined	No. of children with serum neutralizing antibody				
		Triple negative	Type 1	Type 2	Type 3	Types 1, 2, 3
Prior to first dose	91	61 (67)[a]	11 (12)	21 (23)	12 (13)	4 (4)
Thirty days after first dose	50	20 (40)	12 (24)	23 (46)	11 (22)	5 (10)
Thirty days after second dose	33	11 (33)	12 (36)	19 (58)	11 (33)	7 (21)

[a] Figures in parentheses are percentages.

30 days after the second dose of TOPV, 11 (33%) remained triple-antibody negative and 7 (21%) had antibody to all three types of virus (Table 2). At this time, 19 (58%) had serum antibody to type 2 virus, 12 (36%) to type 1, and 11 (33%) to type 3.

The virus titre in vaccines transported to the field each 30 days during the study was greater than 10^5 $TCID_{50}$, compared with the recommended minimum titre of $10^{4.5}$–$10^{6.4}$ as stipulated by the United States Food and Drug Administration.

Enterovirus infection rate among immunized children

Among the 61 children who were triple-antibody negative at the start of the study, 7 (12%) were excreting non-polio-enterovirus before the first dose of vaccine. Among 50 of these children who were not followed up till 30 days after the first dose of vaccine, 20 remained seronegative and among them 3 (15%) had been excreting non-polio-enterovirus at the time of receiving the first dose of vaccine. Among the 30 children who did seroconvert to at least one type of poliovirus, 1 (3%) had been excreting non-polio-enterovirus at the time of the first dose. The difference between these two non-polio-enterovirus infection rates is not statistically significant ($P=0.17$, Fisher's exact test).

Four (7%) of the 61 children who had been triple-antibody negative at the start of the study were excreting poliovirus of vaccine origin at the time of the first dose of vaccine. Thirty days after the first dose of vaccine, 10 (20%) out of 50 children, triple negative at the start, were excreting polio-vaccine virus, an increase which is statistically significant ($P=0.03$, Fisher's exact test). By the 30th day after the second dose of vaccine, the polio-vaccine virus excretion rate among those who were triple-antibody negative at the start had decreased to 9% (3 children). Only one child (out of the 50 examined 30 days after the first dose, and out of the 33 examined 30 days after the second dose) was found to be excreting poliovirus of non-vaccine origin.

Table 3. Non-poliovirus and poliovirus isolates by rectal swab of household contacts of children immunized with TOPV, Yaounde, Cameroon, 1978

	No. of children examined	No. of children with non-polio enterovirus				No. of children with poliovirus of non-vaccine origin	No. of children with poliovirus of vaccine origin
		Total	REO[a]	ADV[b]	NPE[c]		
Prior to first dose in immunized child	109	19 (17)[d]	1	3	15	1 (1)	6 (6)[e]
Thirty days after the first dose	74	11 (15)	1	2	8	2 (3)	10 (14)[e]
Thirty days after the second dose	50	9 (18)	0	1	8	2 (4)	5 (10)

[a] REO = reovirus.
[b] ADV = adenovirus.
[c] NPE = non-polio-enterovirus.
[d] Figures in parentheses are percentages.
[e] Not significant ($P=0.10$ by χ^2 test).

Enterovirus infection rate among household contacts of immunized children

A total of 109 household contacts of immunized children, with a mean age of 37 months (range, 12–59 months), were examined for enteric virus excretion. Among them, 54 (50%) had had one or more doses of TOPV at some time preceding the study. Of the 109 contacts, 19 (18%) were excreting non-polioviruses (isolated by rectal swab) at the time a sibling was given the first dose of vaccine and 6 (6%) were excreting poliovirus of vaccine origin (Table 3); 1 (1%) was excreting poliovirus that was thought to be a non-vaccine strain. On the 30th day after the first dose of vaccine, 11 (15%) of the 74 household contacts who had been followed up were excreting non-polio-virus, 10 (14%) were excreting polio-vaccine virus, and 2 (3%) were excreting non-vaccine poliovirus. The increase among household contacts excreting polio-vaccine virus 30 days after the first dose of vaccine was given to a sibling is not statistically significant ($P=0.10$, by χ^2 test).

DISCUSSION

The estimated annual incidence of paralytic poliomyelitis in Yaounde, Cameroon, decreased by 85% during the first five years of the poliomyelitis control programme. No significant changes in the city's water supply or sanitation system occurred during this time, and the change in incidence is presumed to be the result of continuous and exclusive use of trivalent oral poliovirus vaccine.

The annual incidence of paralytic poliomyelitis was estimated by reviewing the records at the city's major treatment and rehabilitation centre for poliomyelitis. For completeness of surveillance, the records were reviewed till the end of December 1980 so that all cases with onset in 1979, which may have been first seen in consultation during 1980, were registered. Children with acute flaccid paralysis are seldom admitted to the city's hospitals, but are immediately referred to this treatment and rehabilitation centre from outpatient clinics. The first visit to this centre is free of charge, and it is assumed that most children who were referred did attend this first consultation. To evaluate the completeness of surveillance based on the records of the treatment and rehabilitation centre, we reviewed the records at the Yaounde Central Hospital, which has the largest paediatric ward in Yaounde. Only 11 children had been admitted to this ward with a diagnosis of paralytic poliomyelitis or flaccid paralysis during the years 1976–80, confirming the fact that most of the children with paralysis were referred immediately to the treatment and rehabilitation centre, our main surveillance site, and were not admitted to hospital.

Both 1974 and 1975 do not appear to have been epidemic years for poliomyelitis and the decrease in incidence, which began in 1976, is probably due to post-epidemic decrease in children susceptible to the disease. House-to-house lameness surveys conducted in Yaounde in 1979 estimated an average annual incidence of poliomyelitis of 54 per 100 000 for the years 1967 to 1974, which is not significantly different from the rate of 60 per 100 000 established by surveillance in 1974 (*8*, *9*).

Seroconversion rates to one and two doses of trivalent oral poliovirus vaccine in the Yaounde control programme are low when compared with the rates in temperate climates, e.g., more than 75% in the USA after only one dose of oral polio vaccine for all three types of virus (*10*). The vaccine used in the Yaounde study was fully active when assayed, and low activity does not appear to be the cause of the lower seroconversion rates, which are similar to those in neighbouring Nigeria (in 1976) and Ghana (from 1976 to 1978) (*2*, *3*).

Competition with non-polio-enterovirus does not appear to be the cause of the low seroconversion rates in Yaounde. No significant difference was found between infection rates of children who seroconverted and those who did not. The overall non-polio-enterovirus infection rate, 12% among triple-antibody negative children aged 2–11 months and 17% among older siblings, is similar to the rate of 14.7% found in Kenya among children under 4 years of age in 1973 (*11*) but much lower than the 44% found among children less than 10 months old in Ghana in 1975 (*12*). Virus isolation was done by inoculation on primary monkey kidney cells and a continuous line of BGM cells. Cell line MRC5 (human diploid fibroblasts) might have given a greater yield and use of newborn mice might have increased the isolation of coxsackievirus A. Since enterovirus infection rates in Yaounde were determined from rectal swab specimens and during a period of low transmission of diarrhoeal disease, they may have been underestimated. A non-polio-enterovirus infection rate of 9.5%, which is similar to what we found in Yaounde, was obtained in a study of stool samples collected from hospitalized children under 3 years of age in India in 1979 (*13*).

Cross-immunity among the poliovirus types may be a factor in the decrease in annual incidence of paralytic poliomyelitis in Yaounde, despite the low seroconversion rates to all three virus types. This concept is not new. Horstman in 1955 and Salk in 1956 concluded from controlled studies that the likelihood of developing paralysis from poliomyelitis decreased in the presence of type 2 antibody (*14*, *15*). Schonberger in 1979 noted that triple-seronegative

children compared to non-triple-negative children had several-fold higher rates of paralytic poliovirus infection in Burma (*16*). Among the children we studied in Yaounde, antibody to type 2 poliovirus was the most readily formed. Thirty days after the second dose of vaccine, 58% of children had neutralizing antibody to type 2 virus and therefore may have had some immunity to types 1 and 3. In Yaounde, community acceptance of vaccine was low; in 1979, for example, only 35% of children aged 12–23 months had been immunized with three doses of TOPV, as shown in a sample survey. Community spread of vaccine virus with resulting immunization of unvaccinated contacts, a phenomenon suggested in early studies of TOPV, may have contributed to the decrease in paralytic poliomyelitis in Yaounde. In 1959, Gelfand found that 34% of 46 individuals in the USA continued to excrete oral polio-vaccine virus 30 days after immunization (*17*). There is some evidence to support the hypothesis of community spread of the vaccine virus in Yaounde. Among the 61 previously unimmunized 2–11-month-old children studied for seroconversion, 7% were excreting poliovirus which was thought to be of vaccine origin at the start of the study. Among 109 household contacts of these children, 6% were excreting polio-vaccine virus before any of the study subjects received the vaccine. The vaccine virus isolated from these study children and their contacts was presumably the result of community spread from recently immunized children in the ongoing immunization programme although some could have been due to vaccine actually administered to the children, which fact was not known to the parent who gave the history. At 30 days after immunization, 20% of the study children and 14% of their contacts were still excreting vaccine virus and presumably more had been excreting the vaccine virus earlier in this period. The rate of non-vaccine poliovirus excretion remained at a lower level (0–4%) among the immunized children and their contacts throughout the study period. Benyesh-Melnick et al. showed in the 1960s that 13% of the isolates excreted by individuals after immunization with TOPV changed from RCT− to RCT+, and were therefore characterized as non-vaccine virus (*18*). Thus, the possibility exists that some of the poliovirus identified as non-vaccine virus was originally of vaccine origin; we hope to clarify this by further testing by neutralization with monoclonal antibodies, which is significantly more reliable (*19*).

The experience of control programmes using TOPV in other African cities has been similar to that in Yaounde. In Abidjan, Côte d'Ivoire, where TOPV has been used in an uninterrupted government programme since 1979, less than 50% of children aged 12–23 months received three doses of vaccine. Surveillance in this city was based on paediatric hospital admissions, and the seroconversion rates to oral poliovirus vaccine were less than 40% to each of the three types of poliovirus in 1978 (*20*); an 83% reduction in paralytic poliomyelitis was noted, from 6 per 100 000 in 1978 to 1 per 100 000 in 1981 (*1*). In the Gambia, the reduction in paralytic poliomyelitis at sentinel surveillance sites has approached 100%, with 53% immunization coverage among children aged 12–23 months (*1*). Despite these great reductions in paralytic poliomyelitis, large numbers of unimmunized children remain susceptible to the disease, and control programmes must continue their efforts to increase coverage.

Our experience in Cameroon indicates that the evaluation of serum neutralizing antibody after immunization and the estimation of immunization coverage are insufficient criteria for determining the effectiveness of oral poliovirus vaccine in tropical Africa. Complete evaluation of the effectiveness of control programmes using oral vaccine must also include surveillance for changes in the incidence of paralytic disease. Although the decreases in paralytic poliomyelitis in Yaounde with TOPV were steady and sustained, the incidence rates in 1979 remained at an unacceptably high level, similar to those in the USA in the early 1950s, the pre-vaccine era. Increasing the coverage rates with TOPV to levels approaching the goal of 100% by 1990, as recommended by WHO, should lead to even greater reductions in paralytic poliomyelitis.

RÉSUMÉ

VACCIN ANTIPOLIOMYÉLITIQUE BUCCAL EN AFRIQUE TROPICALE: IMPACT PLUS GRAND SUR L'INCIDENCE DE LA PARALYSIE QUE NE LAISSAIENT PRÉVOIR LES ENQUÊTES DE COUVERTURE ET LES TAUX DE SÉROCONVERSION

D'après les données d'une enquête recourant à l'échantillonnage par grappes, 35% au maximum des enfants de 12 à 23 mois auraient reçu trois doses de vaccin antipoliomyélitique buccal (VPO) trivalent au cours des cinq premières années (1975–1980) d'un programme de lutte antipoliomyélitique conduit à Yaoundé (Cameroun). Les

taux de séroconversion après deux doses de VPO trivalent, déterminés pendant cette même période chez 91 enfants âgés de 2 à 11 mois ont montré que, 30 jours après la deuxième dose de vaccin, 58% seulement des enfants présentaient des anticorps dirigés contre le virus de type 2, 36% contre le virus de type 1 et 33% contre le virus de type 3. Malgré la faiblesse du taux de couverture et des taux de séroconversion, l'incidence de la poliomyélite paralytique, estimée d'après les registres d'un centre de traitement et de rééducation pour enfants handicapés à Yaoundé, et confirmée par une enquête sur la claudication dans la collectivité, a baissé de 85% entre 1975 et 1979.

Une étude des coprocultures réalisées chez tous les enfants au moment de l'administration du vaccin permet de proposer plusieurs explications possibles à la baisse spectaculaire de la poliomyélite paralytique. En effet, les résultats des cultures montrent que les taux d'excrétion du virus vaccin augmentaient sensiblement chez les enfants vaccinés, passant de 7% immédiatement avant l'administration de la première dose de vaccin à 20% 30 jours plus tard, ce qui permet de penser que certains des enfants avaient déjà été mis en contact avec le virus vaccin avant d'être eux-mêmes vaccinés et que, une fois vaccinés, ils étaient capables d'excréter le virus, et donc de le propager, pendant les 30 jours suivant la vaccination.

Ces résultats semblent indiquer qu'à elles seules les enquêtes de couverture vaccinale et la détermination des taux de séroconversion ne suffisent pas à déterminer l'efficacité des programmes de lutte contre la poliomyélite faisant appel au vaccin antipoliomyélitique buccal en Afrique tropicale, et qu'il importe aussi de surveiller l'incidence de la forme paralytique de la maladie.

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