Epidemiology and clinical characteristics of acute flaccid paralysis associated with non-polio enterovirus isolation: the experience in the Americas

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The Pan American Health Organization adopted as a goal the interruption of transmission of wild poliovirus from the Americas by 1990. Collection and processing of stool specimens from patients with acute flaccid paralysis (AFP) to identify wild poliovirus is critical for monitoring the success of the eradication programme. In the study described, cases of AFP in children less than 15 years of age reported in the Americas from 1989 to 1991 were evaluated to investigate the epidemiology of AFP associated with the isolation of non-polio enterovirus (NPEV), to characterize their clinical presentation, and to compare their clinical characteristics with those of AFP cases associated with the isolation of wild poliovirus (confirmed as poliomyelitis).

The results show that the notification pattern for AFP associated with NPEV isolates is similar to that for all AFP cases. While AFP associated with NPEV isolates generally differs clinically from confirmed poliomyelitis, 2–21% of cases met one of three case definitions for poliomyelitis. Following the eradication of poliomyelitis, countries can therefore anticipate the continued reporting of cases of AFP that clinically mimic poliomyelitis but which are associated with NPEV. The study also confirms that NPEV circulation is common and that most isolates were from cases that did not resemble poliomyelitis. It is therefore questionable whether characterization of NPEV isolates is essential for global eradication of poliomyelitis and consequently whether allocation of resources for that purpose can be justified.

Introduction

In 1985 the Pan American Health Organization (PAHO) adopted as a goal the interruption of transmission of wild poliovirus in the Americas by 1990 (*1*).[a] The central strategies for attaining this goal were as follows: reaching and maintaining high coverage levels with oral poliovirus vaccine (OPV); strengthening poliomyelitis surveillance; and initiating active outbreak control measures for all reported cases (*2, 3*). National surveillance systems were developed to enable authorities to detect cases of acute flaccid paralysis (AFP) and to apply standardized case investigations for classification.

Because the processing of stool specimens to identify wild poliovirus is crucial for monitoring the success of the programme, a laboratory network for viral isolation was developed by PAHO.[b] Stool specimens collected from AFP patients are processed and the results reported as follows: negative for any enterovirus; positive for wild poliovirus; positive for Sabin-strain poliovirus; positive for non-polio enterovirus (NPEV); or positive for Sabin-strain poliovirus and NPEV. All AFP cases from which wild poliovirus is isolated are automatically confirmed as

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[a] In August 1994, PAHO announced that 3 years had passed since the occurrence of the last case of poliomyelitis associated with wild poliovirus isolation in the Americas. In September 1994, the International Commission for the Certification of Poliomyelitis Eradication in the Americas concluded that wild poliovirus transmission had been interrupted in the Americas (*Weekly epidemiological record*, 1994, **69**: 233–300).

[b] *Manual for the virological investigation of poliomyelitis.* Unpublished document WHO/EPI/CDS/POLIO/90.1, 1990.

poliomyelitis. Cases lacking a wild poliovirus isolate are classified as either poliomyelitis or not poliomyelitis according to their clinical presentation, epidemiological evaluation, and laboratory results.

Since NPEVs circulate commonly throughout the world, isolation of an NPEV could represent naturally occurring background viral circulation and, therefore, not be proof of a causal relationship with the paralysis (*4*). Thus, the isolation of an NPEV from AFP cases does not determine their final classification. The typing of NPEV for purposes of poliomyelitis eradication was not considered useful, since a causal relationship could not be assumed. Nevertheless, NPEVs have been isolated from cases associated with both paralytic disease and with outbreaks that have clinically mimicked poliomyelitis, e.g., coxsackievirus type A7 and enterovirus 71 (*5–9*).

Reports of NPEV causing poliomyelitis-like illness could have implications for poliomyelitis eradication. For example, the presence of such cases could result in needless outbreak vaccination control activities. Conceivably, resources might be needed to develop the laboratory capability to characterize all NPEV isolates from AFP cases and to quantify the probability of causality.

We conducted a study that had the following objectives: description of the epidemiology of AFP cases with NPEV isolates; characterization of the clinical presentation of AFP cases with NPEV isolates; and comparison of the clinical characteristics of AFP cases with NPEV isolates and those with wild poliovirus isolates. The aim was to determine whether cases with NPEV isolates can be confused with those with wild poliovirus isolates and to gain a better understanding of the potential importance of the former for poliomyelitis eradication.

Methods

The PAHO regional database (Poliomyelitis Epidemiologic Surveillance System (PESS)) was used to identify all reported AFP cases in children less than 15 years of age in the Americas with onset of paralysis from 1989 to 1991. In Latin America, AFP is a notifiable disease and each country reports all AFP cases weekly to PAHO. Country case reports include information on clinical presentation, demographic details, and stool specimen results. All stool specimens from AFP cases are tested for viral isolation in accordance with WHO recommendations.[c] Isolates are reported as negative or positive for NPEV and/or poliovirus. Most countries in the Americas have conducted national immunization days during which OPV has been administered, resulting in frequent isolation of Sabin-strain poliovirus; therefore, polioviruses are further characterized as wild or Sabin-strain by the regional reference laboratory.[d]

We characterized AFP cases with NPEV isolates by age, sex, and clinical diagnosis, and compared AFP cases with NPEV isolates with those that were positive for Sabin-strain virus or wild poliovirus, and those with negative stool specimens. The secular and seasonal reporting trends were also evaluated for each group.

Because clinical manifestations can vary with age, comparisons between cases with NPEV isolates and cases with wild poliovirus were performed for two age groups: all AFP cases in children less than 15 years of age; and AFP cases in children less than 5 years of age only. A third group was also evaluated: AFP cases in children less than 5 years of age with "other" diagnoses, such as Guillain-Barré syndrome or trauma. For the evaluation of clinical characteristics, only the 838 cases with NPEV isolates without concurrent Sabin-strain isolates were analysed, in order to eliminate any potential impact of a Sabin-strain poliovirus infection on the clinical presentation.

In addition, the proportion of AFP cases aged less than 5 years with NPEV isolates that met three clinical case definitions for poliomyelitis was compared with the proportion of AFP cases with wild poliovirus isolates that met those definitions.[e] The case definitions chosen had previously been shown to be important in the differential diagnosis of poliomyelitis (*10*).

The computer program Epi Info was used for all the data analyses (*11*). Tests of significance for the presence of clinical signs and symptoms in the study groups were carried out for all AFP cases and for only those cases with complete information for a particular sign or symptom. Since the results were generally consistent for the two groups (approximately 90% agreement) the clinical findings presented are those for all AFP cases.

[c] See footnote *b*, p. 597.

[d] *Procedural guide for polioviruses and enteroviruses: isolation, identification and serology.* Pan American Health Organization, unpublished document EPI/TAG/86/006, 1988.

[e] The clinical case definitions used were as follows: fever at onset of paralysis and progression of paralysis of 4 days' duration; fever at onset of paralysis and residual paralysis at 60 days; and fever at onset of paralysis with progression of paralysis of 4 days' duration and with residual paralysis at 60 days.

Results

Epidemiology, clinical diagnosis, and sex and age distribution of AFP cases by stool result

A total of 5979 AFP cases in children less than 15 years of age were reported to PAHO over the period 1989–91 and stool specimens were collected from 4986 (83%) of them (Table 1). Enteroviruses were isolated from 1251 (25%) of these stool specimens: wild poliovirus from 49 (4%); Sabin-strain poliovirus from 300 (24%); and NPEV from 902 (72%). Mixed isolates of NPEV and Sabin-strain poliovirus were present in 64 children.

All subregions of the Americas reported AFP cases with NPEV isolates over the 3-year study period (Fig. 1). When evaluated by month of onset of paralysis, the notification pattern for such cases followed that for all AFP cases, with an increased number of reports during the summer months (Fig. 2).

The commonest diagnosis for AFP cases with NPEV isolates was Guillain-Barré syndrome (334 of 838 isolates, (40%)). However, for a substantial proportion the diagnosis was listed as unknown (189 (23%)) or "other" (272 (32%)). Over the 3-year study period only 1–2% of cases per year were diagnosed as poliomyelitis.

AFP cases with NPEV isolates did not differ by clinical diagnosis from AFP cases with negative stool specimens (Table 2). However, compared to AFP cases with wild poliovirus, they were more likely to be diagnosed as Guillain-Barré syndrome (40% versus 4%, $P < 10^{-6}$).

The distribution of viral isolates differed by age (Fig. 3) but not by sex. For example, NPEV isolates were less likely to be reported than wild poliovirus isolates from children younger than 1 year (7% versus 29%, $P < 10^{-6}$), but were twice as likely to be reported as wild poliovirus isolates from children in the range 5–9 years (21% versus 10%, $P = 0.06$).

Clinical comparison of AFP cases with NPEV isolates and those with wild poliovirus isolates

Children with NPEV isolates were less likely than those with wild poliovirus isolates to have fever at onset of paralysis (30% versus 73%, $P < 10^{-6}$), residual paralysis (24% versus 69%, $P < 10^{-6}$), atrophy (9% versus 41%, $P < 10^{-6}$), or a history of prodromal fever (37% versus 51%, $P = 0.04$) (Table 3), but were more likely to have ascending paralysis (32% versus 18%, $P = 0.045$). These differences persisted when stratified by age and clinical diagnosis. Thus, regardless of diagnosis, under-15-year-olds and under-5-year-olds with NPEV isolates were less likely than those with wild poliovirus isolates to report fever at onset of paralysis, residual paralysis, and atrophy ($P < 10^{-6}$). In addition, children with NPEV isolates were less likely to meet the criteria for the three different clinical case definitions we evaluated than those with wild poliovirus isolates (Table 4). However, among NPEV cases with any diagnosis or with a diagnosis of "other", 2–21% met one of the three clinical case definitions and, therefore, could be clinically confused with poliomyelitis.

Discussion

This evaluation demonstrates that isolation of NPEV from AFP cases is common in the Americas and that notification of such cases follows the trends for all AFP cases. Over the period 1989–91, 72% (200–300 per year) of all viral isolates from AFP cases were NPEV. Unfortunately, it is not possible to determine whether such isolates were causally related to the paralysis or represent background enterovirus circulation. Nevertheless, countries can expect continued reporting of AFP cases with NPEV isolates.

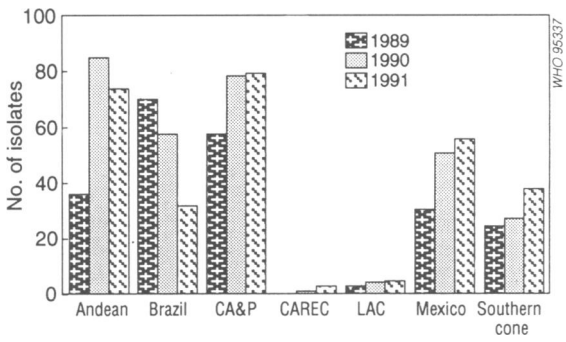
Several NPEVs have been associated anecdotally with paralytic disease: coxsackievirus (types A4,

Table 1: **Results of virus isolation from stool samples collected from under-15-year-olds with acute flaccid paralysis (AFP), by year, in the Americas, 1989–91**

	Total with AFP	Total with stool sample	Isolate: Wild poliovirus	Sabin-strain poliovirus	NPEV[a]	NPEV and Sabin-strain poliovirus
1989	1912	1595	24 (6)	122 (31)	223 (56)[b]	27 (7)
1990	2019	1707	17 (4)	92 (21)	306 (69)	26 (6)
1991	2044	1684	8 (2)	86 (21)	309 (75)	11 (3)
Total	5979	4986	49 (4)	300 (24)	838 (67)	64 (5)

[a] NPEV = non-polio enterovirus.
[b] Figures in parentheses are percentages of the total number of AFP cases with enterovirus isolates.

Fig. 1. **Number of non-polio enterovirus isolates among cases of acute flaccid paralysis, by subregion of the Americas, 1989–91** (CA & P = Central America and Panama; CAREC = Caribbean countries; LAC = Latin American Caribbean; Southern cone = Southern cone of Latin America).



6, 7, 9, 11, 14 and 21; and B1, 2, 3, 4, 5 and 6) echovirus (types 1, 2, 3, 4, 6, 7, 9, 11, 14, 16, 18, 19 and 30) and enterovirus (types 70 and 71) (*12*). Clinically the patients concerned were reported to have signs and symptoms indicative of poliomyelitis: fever at onset of paralysis and rapid progression of paralysis.

However, our findings suggest that AFP cases with NPEV isolates differ in age and several clinical characteristics from those with wild poliovirus isolates. Those with NPEV isolates were older and less likely to have fever during onset of paralysis, residual paralysis, and atrophy, but were more likely to be diagnosed as Guillain-Barré syndrome. These data suggest that, as a group, AFP cases with NPEV isolates are generally unlikely to be confused with poliomyelitis. However, the data also indicate that the

Fig. 2. **Number of cases of acute flaccid paralysis (AFP) and number of AFP cases associated with non-polio enterovirus isolates (NPEV), by month of onset, in the Americas, 1989–91.**

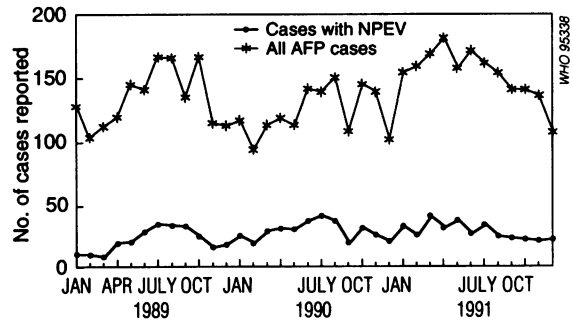


Fig. 3. **Age distribution of cases of acute flaccid paralysis, by virological result of stool specimen, in the Americas, 1989–91** (NPEV = non-polio enterovirus).

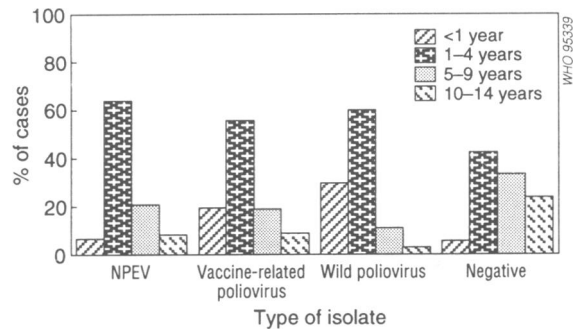


Table 2: **Results of virus isolation from stool samples, by clinical diagnosis, collected from under-15-year-olds with acute flaccid paralysis in the Americas, 1989–91**

		Clinical diagnosis (%):						
Isolate	*n*	Poliomyelitis	GBS[a]	Trauma	TM[b]	Tumour	Other	Unknown
Negative	3720	2	45	1	2	1	33	17
Wild poliovirus	49	88	4	0	2	0	0	6
Sabin-strain poliovirus	300	13	32	1	2	2	30	20
NPEV[c]	838	1	40	1	1	2	32	23
NPEV and Sabin-strain poliovirus	64	13	23	2	2	0	48	13

[a] GBS = Guillain-Barré syndrome.
[b] TM = Transverse myelitis.
[c] NPEV = non-polio enterovirus.

Table 3: **Comparison of clinical characteristics of cases of acute flaccid paralysis (AFP) associated with non-polio enterovirus (NPEV) isolates with those from cases of AFP associated with wild poliovirus isolates from under-15-year-olds in the Americas, 1989–91**

Sign/symptom	Proportion (%) of cases associated with: NPEV (n = 838)	Wild poliovirus (n = 49)	P-value
Fever at onset of paralysis	30	73	$<10^{-6}$
Residual paralysis	24	69	$<10^{-6}$
Atrophy	9	41	$<10^{-6}$
Prodromal fever	37	51	0.04
Ascending paralysis	32	18	0.045
Meningeal irritation	4	8	0.1
Prodromal respiratory symptoms	21	18	0.7
Prodromal gastrointestinal symptoms	21	29	0.2
Muscle pain	39	29	0.1
Progression of paralysis of <4 days' duration	52	65	0.07
Cranial nerve involvement	10	8	0.6
Respiratory involvement	8	2	0.1

NPEV group is not homogeneous; up to 18% mimicked poliomyelitis clinically by exhibiting fever at onset of paralysis and rapid progression of paralysis.

It should be noted that these data were collected within an ongoing AFP surveillance system in the Americas which was not designed to evaluate NPEVs as a cause of AFP, since its focus was on poliomyelitis and polioviruses. NPEV typing, which requires considerable effort, was therefore not performed. Furthermore, the surveillance system only detects NPEVs in patients with AFP; hence, the data do not address the question of NPEV circulation directly. It is important to note that different NPEVs can circulate simultaneously throughout a community or region and mixed infections are common, making a clinical evaluation difficult to interpret (*12*). At the same time, different NPEVs can cause similar nonparalytic clinical manifestations, while a single serotype can cause different clinical manifestations.

This study suggests that as poliomyelitis eradication is achieved, AFP cases with fever at onset of paralysis and residual paralysis and with stool specimens negative for wild poliovirus but positive for NPEV will continue to be detected. The data also confirm that NPEV circulation is common and that isolates may be obtained from persons with AFP whose clinical findings do not resemble poliomyelitis. It is therefore questionable whether characterization of NPEV isolates is essential for global eradication of poliomyelitis and, consequently, whether allocation of resources from the global poliomyelitis eradication programme for that purpose can be justified.

Nevertheless, selective characterization of NPEV isolates from those patients with AFP and residual paralysis or atrophy, in conjunction with virological evaluation of appropriate community controls, could indicate which NPEVs are causally associated with paralytic disease. Currently, there is strong evidence of such a relationship for enterovirus 71 (*4, 5, 7, 8*).

The results of this study indicate that although characterization of NPEV isolates is not crucial for poliomyelitis eradication, it could provide a better understanding of the epidemiology of paralysis caused by non-polio enteroviruses and potentially contribute to the development of vaccines for the prevention of such paralysis.

Table 4 : **Proportion of cases of acute flaccid paralysis (AFP) in under-5-year-olds with non-polio enterovirus isolates and those with wild poliovirus isolates that met three clinical case definitions, in the Americas, 1989–91**

Case definition	% of all diagnoses: NPEV (n = 588)	Wild poliovirus (%) (n = 43)	P-value	% diagnosed as "other": NPEV (n = 209)	Wild poliovirus (%) (n = 43)	P-value
Fever at onset of paralysis and progression of paralysis of <4 days' duration	18	47	<0.01	21	47	<0.01
Fever at onset of paralysis and residual paralysis	7	58	$<10^{-6}$	6	58	$<10^{-6}$
Fever at onset of paralysis with progression of paralysis of <4 days' duration and residual paralysis	3	26	$<10^{-6}$	2	26	$<10^{-6}$

Résumé

Epidémiologie et aspects cliniques de la paralysie flasque aiguë associée à l'isolement d'entérovirus non poliomyélitiques: l'expérience des Amériques

En 1985, l'Organisation panaméricaine de la Santé (OPS) a adopté comme but l'éradication de la transmission des poliovirus sauvages indigènes dans les Amériques en 1990. Le recueil et le traitement d'échantillons de selles de malades atteints de paralysie flasque aiguë (PFA) afin d'identifier le poliovirus sauvage est une étape critique de la surveillance des résultats du programme d'éradication. Les échantillons sont classés en négatifs pour tous les entérovirus, positifs pour le poliovirus sauvage, positifs pour le poliovirus de souche Sabin, positifs pour les entérovirus non poliomyélitiques (EVNP), ou positifs pour le poliovirus de souche Sabin et les EVNP. Tous les cas de PFA associés à l'isolement de poliovirus sauvage ont été confirmés comme poliomyélitiques, alors que les cas de PFA associés aux EVNP ont un diagnostic final qui dépend des aspects cliniques et épidémiologiques de la maladie. Du point de vue du programme d'éradication de la poliomyélite, l'intérêt de caractériser les isolements d'EVNP selon le type est douteux, et ce typage n'est pas pratiqué actuellement. Toutefois, des EVNP ont été associés à des cas ressemblant cliniquement à une poliomyélitique paralytique.

Afin de déterminer si les cas de PFA avec isolement d'EVNP peuvent être confondus avec les cas correspondant à des isolements de poliovirus sauvage, et afin de mieux connaître l'importance potentielle de ces cas du point de vue de l'éradication de la poliomyélite, nous avons évalué l'ensemble des cas de PFA avec isolement d'EVNP rapportés dans les Amériques chez des enfants de moins de 15 ans dont la paralysie a débuté en 1989–1991. Les cas de PFA avec isolement d'EVNP ont été comparés aux cas de PFA avec isolement de poliovirus sauvage dans le même groupe d'âge.

Sur les 1676 isolements de virus obtenus chez les 5979 cas de PFA rapportés sur la période étudiée dans les Amériques, 72% étaient des EVNP. Les modalités de notification des cas de PFA avec EVNP étaient les mêmes que pour l'ensemble des cas de PFA. Les cas de PFA avec EVNP différaient des cas avec isolement de poliovirus sauvage par l'âge, mais non par la répartition selon les sexes. De plus, les sujets porteurs d'EVNP, quel que soit leur âge, avaient moins souvent que les sujets porteurs de poliovirus sauvage de la fièvre au début de la paralysie (30% contre 73%, $p<10^{-6}$), une paralysie résiduelle (24% contre 69%, $p<10^{-6}$) ou une atrophie lors de la visite de suivi (9% contre 41%, $p<10^{-6}$).

D'après ces résultats, les cas de PFA avec isolement d'EVNP diffèrent cliniquement, en tant que groupe, des cas de poliomyélite. Toutefois, 2 à 21% de l'ensemble des cas de PFA avec isolement d'EVNP satisfont à l'une ou l'autre des trois définitions du cas clinique de poliomyélite. Les pays peuvent donc s'attendre à une poursuite des notifications de cas de PFA ressemblant cliniquement à des cas de poliomyélite mais associés à des EVNP, même après l'éradication de la poliomyélite.

La présente étude confirme également que la circulation des EVNP est courante et que la plupart des isolements d'EVNP ont été réalisés chez des sujets dont l'état clinique n'évoque pas une poliomyélite. On peut par conséquent se demander si la caractérisation des isolements d'EVNP est indispensable dans le cadre des activités d'éradication mondiale de la poliomyélite et si l'attribution de ressources à cet effet par le programme mondial d'éradication de la poliomyélite est justifiée.

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