

INTRAMUSCULAR INJECTIONS WITHIN 30 DAYS OF IMMUNIZATION WITH ORAL POLIOVIRUS VACCINE — A RISK FACTOR FOR VACCINE-ASSOCIATED PARALYTIC POLIOMYELITIS

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Abstract Background. In Romania the rate of vaccine-associated paralytic poliomyelitis is for unexplained reasons 5 to 17 times higher than in other countries. Long ago it was noted that intramuscular injections administered during the incubation period of wild-type poliovirus infection increased the risk of paralytic disease (a phenomenon known as "provocation" poliomyelitis). We conducted a case-control study to explore the association between intramuscular injections and vaccine-associated poliomyelitis in Romania.

Methods. The patients were 31 young children in whom vaccine-associated paralytic poliomyelitis developed from 1988 through 1992. Eighteen were vaccine recipients, and 13 had acquired the disease by contact with vaccine recipients. Each of these children was matched with up to five controls according to health center, age, and in the case of vaccine recipients, history of receipt of the live attenuated oral poliovirus vaccine. Data were abstracted from medical records that documented the injections administered in the 30 days before the onset of paralysis.

Results. Of the 31 children with vaccine-associated disease, 27 (87 percent) had received one or more intramuscular injections within 30 days before the onset of paralysis, as compared with 77 of the 151 controls (51 percent) (matched odds ratio, 31.2; 95 percent confidence interval, 4.0 to 244.2). Nearly all the intramuscular injections

were of antibiotics, and the association was strongest for the patients who received 10 or more injections (matched odds ratio for ≥ 10 injections as compared with no injections, 182.1; 95 percent confidence interval, 15.2 to 2186.4). The risk of paralytic disease was strongly associated with injections given after the oral poliovirus vaccine, but not with injections given before or at the same time as the vaccine (matched odds ratio, 56.7; 95 percent confidence interval, 8.9 to infinity). The attributable risk in the population for intramuscular injections given in the 30 days before the onset of paralysis was 86 percent (95 percent confidence interval, 66 to 95 percent); that is, we estimate that 86 percent of the cases of vaccine-associated paralytic poliomyelitis in this population might have been prevented by the elimination of intramuscular injections within 30 days after exposure to oral poliovirus vaccine.

Conclusions. Provocation paralysis, previously described only for wild-type poliovirus infection, may rarely occur in a child who receives multiple intramuscular injections shortly after exposure to oral poliovirus vaccine, either as a vaccine recipient or through contact with a recent recipient. This phenomenon may explain the high rate of vaccine-associated paralytic poliomyelitis in Romania, where the use of intramuscular injections of antibiotics in infants with febrile illness is common. (N Engl J Med 1995;332:500-6.)

BETWEEN 1970 and 1984, Romania participated in a study of the safety of the live attenuated oral poliovirus vaccine (OPV) coordinated by the World Health Organization. Several reports from this study showed that the risk of vaccine-associated paralytic poliomyelitis in Romania was 5 to 17 times higher than in any of the other 12 countries in the study.¹⁻⁴ A commonly suggested explanation for this high rate of vaccine-associated disease was an increased neurovirulence of the OPV manufactured in Romania, which was the only poliovirus vaccine used in the country.² The Romanian vaccine underwent extensive evaluation by independent laboratories, however, and met all safety standards.³ The unusually high risk of vaccine-associated poliomyelitis in Romania remained unexplained for more than 15 years.⁴ In November 1990, Romanian-manufactured OPV was replaced throughout the country with OPV imported from a Western European manufacturer. During the next two years 23 cases of vaccine-associated paralytic poliomyelitis were confirmed in Romania — a rate of 1 case per

196,000 doses of OPV distributed.⁵ This was similar to the rate during the previous six years, when Romanian-manufactured OPV was used exclusively (1 case per 178,000 doses). Thus, neither epidemiologic data nor laboratory data indicated that increased neurovirulence of the Romanian OPV was a likely explanation for the high risk of vaccine-associated paralysis.

Because intramuscular injections administered during the incubation period of wild-type poliovirus in infected persons increase the risk of paralytic disease (a phenomenon known as "provocation" poliomyelitis)⁶⁻⁸ and because Romanian children with vaccine-associated poliomyelitis had frequently received injections during the month before the onset of paralysis, we conducted a case-control study to explore the association between intramuscular injections and vaccine-associated paralytic poliomyelitis in Romania.

METHODS

Identification of Cases

Fifty-one confirmed cases of paralytic poliomyelitis were eligible for study. All the children met previously established epidemiologic and laboratory criteria^{9,10} for vaccine-associated disease in persons exposed to OPV either as vaccine recipients or their contacts, with onset between January 1988 and December 1992. The children who had received OPV had onset of paralysis 4 to 30 days after the receipt of the vaccine.⁵ Children who acquired the disease by contact with vaccine recipients had onset of paralysis within 60 days of the start of a mass OPV-vaccination campaign in their area of residence; poliovirus was isolated from stool specimens obtained from these

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children within four weeks of onset and was characterized as related to the OPV by assays based on monoclonal antibodies and molecular-probe techniques.^{11,12} Ten cases (in 6 vaccine recipients and 4 contacts) in children living in orphanages or nutrition-rehabilitation centers and 10 cases (in 2 vaccine recipients and 8 contacts) in children for whom a precise date of onset of paralysis could not be determined were excluded from the case-control study. The remaining 31 children with paralytic poliomyelitis — 18 who had received the vaccine and 13 who acquired the disease by contact — were enrolled in the study.

Selection of Controls

Controls were selected at the dispensary (health center) at which each case patient regularly received primary care. Because all newborns in Romania are entered chronologically in the vaccination register at their local dispensary, the register was used for the selection of neighborhood controls. The controls were those listed in the vaccination register immediately before or after the case patients. In addition, control children had to be active patients at the dispensary. The controls were matched for age within one month for case children less than four months of age, and within three months for older children. The first five controls who met the matching criteria for each case patient were selected. With the date of onset of paralysis in the case patient as the reference date, the controls selected for the case patients who were vaccine recipients had to have received a dose of OPV in the same vaccination campaign as the case patient (i.e., the controls for the vaccine recipients with paralysis received a dose of OPV 4 to 30 days before the reference date). Children who acquired poliomyelitis by contact and their controls were not matched according to the number of doses of OPV they had received, because in many instances the case patients had been ill at the time of the vaccination campaign and therefore were not vaccinated, whereas the age-matched controls received OPV during the campaign. Five controls were matched to each of the case children, except for one with a contact-acquired case of poliomyelitis who lived in a remote area; only one control could be identified for this child.

Collection of Data

Until children enter school at four to six years of age, their medical records are kept at the local dispensary. The following information was obtained from the medical records of both case patients and controls: date of birth, birth weight, sex, health status at the routine visit at one month of age, dates and reasons for all hospitalizations since birth, and dates of all visits to the dispensary during the 30 days before the onset of paralysis for the case children or the reference date for controls. For both hospitalizations and dispensary visits, the primary and secondary diagnoses recorded by the pediatrician, as well as all medications prescribed by a physician and their route of administration, were noted. Sociodemographic data, such as the family's type of housing and the occupation and age of the parents, were also noted. Dates of vaccination with OPV and with diphtheria and tetanus toxoids and pertussis vaccine (DTP) were transcribed from the vaccination register. The clinic staff members were interviewed to obtain additional information about socioeconomic conditions in the children's homes (such as the method of sewage disposal, source of potable water, and number of siblings in the household).

Statistical Analysis

Differences between proportions were tested with chi-square statistics,¹³ and differences between medians were tested by the Wilcoxon rank-sum statistic.¹⁴ Matched odds ratios and two-sided 95 percent confidence intervals were calculated by conditional logistic regression, which accounts for the matched design.¹⁵ Because of the small numbers of subjects, it was not always possible to obtain a conditional maximum-likelihood estimate of the odds ratio. In such situations, we calculated the median unbiased estimate of the odds ratio and the exact confidence interval.¹⁶⁻¹⁸

For cases of paralytic poliomyelitis in vaccine recipients, we estimated the risk of paralysis associated with intramuscular injections (≥ 1 injection vs. none) in relation to the date of receipt of OPV: before the receipt of OPV, at the same time as the receipt of OPV (the time when the DTP vaccine was given), or after the receipt of OPV. For both cases in vaccine recipients and those acquired by contact,

we estimated the risk of vaccine-associated poliomyelitis for one-week intervals during the 30 days before the onset of paralysis in order to determine whether injections given at certain times were more likely to be associated with an increased risk of disease.

In approximately one third of the cases of paralytic poliomyelitis in children, the illness is biphasic. A so-called minor illness, characterized by malaise, fever, sore throat, and gastrointestinal symptoms and lasting for a few hours to a few days, precedes the paralytic phase by one to seven days.¹⁹ To eliminate the effect of intramuscular injections administered as a consequence of this minor illness, the association between intramuscular injections and vaccine-associated poliomyelitis was determined only for case patients with no preceding minor illness and for their matched controls.

To assess the potential effect of eliminating injections on the incidence of vaccine-associated paralytic poliomyelitis in Romania, we calculated the attributable risk in the population¹³ and the logit-based 95 percent confidence interval²⁰ for any intramuscular injection given within 30 days before the onset of paralysis in the case patients. In this instance, the population attributable risk is a measure of the percentage of cases of vaccine-associated paralytic poliomyelitis that might have been prevented in this population if no intramuscular injections had been given during the 30-day period.

RESULTS

The children with poliomyelitis who had received the OPV and their controls were similar in age, sex, and birth weight, as were the children with disease acquired by contact and their controls (Table 1). Seventeen of 18 children with poliomyelitis who had received the vaccine (94 percent) had onset of paralysis after their first dose of OPV. Children who contracted the disease from contacts were more likely not to have been vaccinated than their age-matched controls (54 percent vs. 8 percent) (Table 1). One to four years after the onset of acute poliomyelitis, none of the children with the disease were known to have human immunodeficiency virus (HIV) infection, and none had died.

Risk Factors for Vaccine-Associated Paralytic Poliomyelitis

Among the vaccine recipients with poliomyelitis and their controls, the matched odds ratios for socioeconomic variables and prior health status were not significantly different from 1.0 (Table 2). All 18 children with vaccine-associated paralytic poliomyelitis had received one or more intramuscular injections within the 30 days

Table 1. Characteristics of Children with Vaccine-Associated Paralytic Poliomyelitis and Their Respective Controls.

CHARACTERISTIC	VACCINE RECIPIENTS		CONTACTS	
	CASES (N = 18)	CONTROLS (N = 90)	CASES (N = 13)	CONTROLS (N = 61)
Age — mo				
Median	5	5	9	10
Range	3–17	2–17	4–46	1–46
Sex — % male	56	58	69	57
Birth weight — kg				
Median	3.2	3.2	3.0	3.1
Range	2.6–4.0	1.9–4.4	0.9–3.2	2.0–4.4
Doses of OPV				
— no. (%) [*]				
0	0	0	7 (54)	5 (8)
1	17 (94)	77 (86)	1 (8)	16 (26)
2	0	8 (9)	3 (23)	21 (34)
≥ 3	1 (6)	5 (6)	2 (15)	19 (31)

^{*}P = 0.42 for the comparison between vaccine recipients with poliomyelitis and their controls, and P < 0.01 for the comparison between children with poliomyelitis acquired by contact and their controls, both by the chi-square test. Because of rounding, percentages do not always total 100.

Table 2. Risk Factors for Vaccine-Associated Paralytic Poliomyelitis in Vaccine Recipients and Contacts and the Controls.*

RISK FACTOR	VACCINE RECIPIENTS			CONTACTS		
	CASES (N = 18)	CONTROLS (N = 90)	MATCHED ODDS RATIO (95% CI)	CASES (N = 13)	CONTROLS (N = 61)	MATCHED ODDS RATIO (95% CI)
	no. (%)			no. (%)		
Socioeconomic variables						
Type of toilet (latrine vs. water closet)†	9 (50)	47 (52)	0.8 (0.1–4.3)	10 (77)	44 (75)	1.0 (0.02–41.2)
Water source (well vs. piped)†	6 (33)	35 (39)	0.4 (0.1–3.3)	7 (54)	36 (61)	0.4 (0.1–3.3)
Siblings <5 years of age (any vs. none)‡	7 (39)	34 (38)	1.0 (0.4–3.0)	6 (50)	27 (47)	1.2 (0.4–4.2)
Gypsy (yes vs. no)	2 (11)	12 (13)	0.8 (0.1–4.4)	1 (8)	8 (13)	0.5 (0.0–3.5)§
No. of persons per room (median)	1.7	1.7	—¶	1.6	1.5	—¶
Prior health status						
Healthy at 1 month of age (yes vs. no)	17 (94)	85 (94)	1.0 (0.1–9.2)	10 (77)	56 (92)	0.4 (0.1–1.8)
Hospitalized 0–30 days before paralysis (yes vs. no)	2 (11)	1 (1)	8.2 (0.6–∞)§	5 (38)	1 (2)	25.0 (2.9–214.0)
Acute non-polio illness 0–30 days before paralysis (yes vs. no)**	8 (44)	28 (31)	2.0 (0.6–6.4)	10 (77)	14 (23)	21.0 (2.6–173.4)
Intramuscular injections						
No. of injections 0–30 days before paralysis						
0	0	31 (34)	1.0††	4 (31)	43 (70)	1.0††
1	6 (33)	47 (52)	4.9 (0.6–∞)§	1 (8)	9 (15)	3.5 (0.2–59.6)
2–9	4 (22)	9 (10)	12.8 (1.2–∞)§	1 (8)	7 (11)	9.6 (0.3–262.4)
≥10	8 (44)	3 (3)	58.0 (7.6–∞)§	7 (54)	2 (3)	85.9 (4.5–1650)
Any injection (yes vs. no)	18 (100)	59 (66)	17.0 (2.5–∞)§	9 (69)	18 (30)	18.1 (2.1–155.2)

*CI denotes confidence interval. The odds ratios for each risk factor were adjusted for matched sets by conditional logistic regression. Because of rounding, percentages do not always total 100.

†Information was not available for two contact controls.

‡Information was not available for one contact case child and four contact controls.

§The odds ratio and confidence interval were calculated by exact conditional logistic regression.

¶P = 0.81 by the Wilcoxon rank-sum test for the difference between the medians.

||P = 0.74 by the Wilcoxon rank-sum test for the difference between the medians.

**Excluding febrile illnesses 0 to 9 days before the onset of paralysis that were compatible with the minor illness of poliomyelitis.

††Reference value.

before the onset of paralysis, as compared with 59 of their 90 controls (66 percent) (matched odds ratio, 17.0; 95 percent confidence interval, 2.5 to infinity). The matched odds ratio for vaccine-associated poliomyelitis in recipients of OPV increased with the number of intramuscular injections.

Socioeconomic variables were similarly distributed among the children with poliomyelitis contracted from contacts and their controls (Table 2). The matched odds ratios for hospitalization and acute illness other than poliomyelitis, both within 30 days before the onset of paralysis, were significantly elevated, however. Nine of 13 children with contact-derived cases of poliomyelitis (69 percent) and 18 of 61 controls (30 percent) received one or more intramuscular injections up to 30 days before the onset of paralysis (matched odds ratio, 18.1; 95 percent confidence interval, 2.1 to 155.2). The matched odds ratio for paralytic poliomyelitis among children who acquired the disease by contact with vaccine recipients increased with an increasing number of intramuscular injections.

An analysis of the data on all 31 case children and their matched controls suggested a dose-response relation between the number of intramuscular injections and the risk of vaccine-associated paralytic poliomyelitis (Fig. 1); the highest risk was among case children who had received 10 or more intramuscular injections

within 30 days before the onset of paralysis (matched odds ratio, 182.1; 95 percent confidence interval, 15.2 to 2186.4).

Intramuscular Injections

Twenty-seven of 31 case children (87 percent) received one or more intramuscular injections within 30 days before the paralysis began, as compared with 77 of 151 controls (51 percent) (matched odds ratio, 31.2; 95 percent confidence interval, 4.0 to 244.2). A total of 454 intramuscular injections were given to 27 children in whom paralytic poliomyelitis subsequently developed (mean, 16.8 injections per child), as compared with a total of 212 injections received by the 77 exposed controls (mean, 2.8 injections). Of the 454 injections given to case children, 256 (56 percent) were of penicillin G, 177 (39 percent) were of other antibiotics (kanamycin, ampicillin, or gentamicin), 16 (4 percent) were of DTP vaccine, and 5 (1 percent) were of vitamin D. Of the 212 injections given to control children, 97 (46 percent) were of penicillin G, 24 (11 percent) were of other antibiotics, 62 (29 percent) were of DTP vaccine, and 29 (14 percent) were of vitamin D.

Antecedent Illnesses

Antecedent illness was defined as an illness resulting in a visit to the dispensary within the 30 days be-

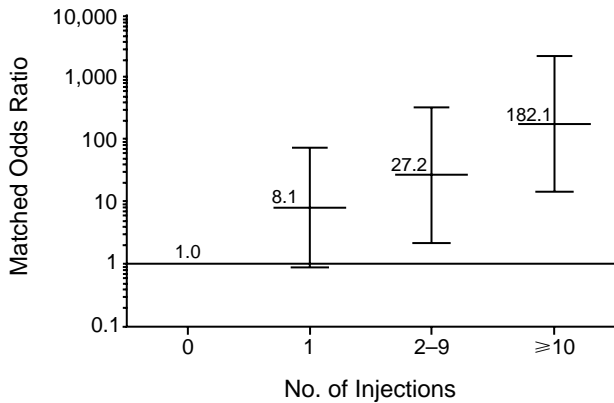


Figure 1. Effect of the Number of Intramuscular Injections on the Risk of Vaccine-Associated Paralytic Poliomyelitis.

The values shown are matched odds ratios and 95 percent confidence intervals. The injections were given within the 30 days before the onset of paralysis in the case children or the reference date in the controls.

fore the onset of paralysis for the case children or before the reference date for controls. Ten of 31 case children (32 percent) had the minor illness of poliomyelitis before the paralytic phase. Two of the 10 case children with such a minor illness also had a lower respiratory tract illness (pneumonia) before the onset of paralysis. Of the remaining 21 children who had poliomyelitis without a minor illness, 5 had pneumonia, 8 had other illnesses (mainly upper respiratory tract infections), and 1 had both pneumonia and another illness.

When we restricted the analysis to the 21 case children without the minor illness and their matched controls, a strong association between intramuscular injections (any vs. none) and the risk of vaccine-associated paralysis was evident (matched odds ratio, 19.7; 95 percent confidence interval, 2.4 to 158.1). For each additional intramuscular injection administered to this group of case children, the risk of paralysis increased by 13 percent (matched odds ratio, 1.13; 95 percent confidence interval, 1.04 to 1.22). To test the hypothesis that intramuscular injections given as therapy for an antecedent illness were not themselves associated with paralytic disease, an analysis was performed using data only on the 24 case children and 42 controls who had an antecedent illness. In this analysis, the receipt of one or more intramuscular injections within 30 days before the onset of paralysis remained significantly associated with the risk of paralysis (matched odds ratio, 9.5; 95 percent confidence interval, 1.2 to infinity).

Timing of Injections Given within 30 Days before the Onset of Paralysis

Intramuscular injections administered after the receipt of OPV were associated with a very high risk of vaccine-associated paralysis (matched odds ratio, 56.7; 95 percent confidence interval, 8.9 to infinity) (Table 3). Injections given before the receipt of OPV, and DTP vaccine administered simultaneously with OPV, were not associated with a significantly in-

creased risk of paralysis. For intramuscular injections administered after the receipt of OPV and before the onset of paralysis, the median interval between the receipt of OPV and the injection was 16 days (range, 9 to 30).

The risk of vaccine-associated poliomyelitis in vaccine recipients was highest for injections given 0 to 7 days and 15 to 21 days before the onset of paralysis (Table 4). The risk of vaccine-associated poliomyelitis contracted from a vaccine recipient was highest for injections given 8 to 14 days before the onset of paralysis and was also significantly elevated for the periods 15 to 21 days and 22 to 30 days before the onset of paralysis.

Effect of Substance Injected

Because matched odds ratios, stratified according to the substance injected, were similar for the vaccine recipients with paralytic poliomyelitis and those who acquired the disease by contact, the two groups were combined. The receipt of penicillin G (any injection vs. none) was strongly associated with an increased risk of paralysis (matched odds ratio, 62.3; 95 percent confidence interval, 8.2 to 475.5), as was the receipt of other antibiotics (any injection vs. none) (matched odds ratio, 40.0; 95 percent confidence interval, 5.0 to 319.8). Penicillin and other antibiotics were administered as courses of therapy (i.e., two, three, or four injections per day for a specified number of days) rather than as single injections. The matched odds ratio for each additional injection of penicillin G (modeled as a continuous variable) was 1.20 (95 percent confidence interval, 1.09 to 1.33), suggesting a 20 percent increase in risk of paralysis for each additional injection of penicillin G. The corresponding additional risk per injection for other antibiotics was 18 percent (matched odds ratio, 1.18; 95 percent confidence interval, 1.04 to 1.34).

Three of 13 children with poliomyelitis acquired by contact (23 percent) and 10 of their 61 controls (16 percent) received DTP within 30 days before the onset of paralysis (matched odds ratio, 2.6; 95 percent confidence interval, 0.3 to 20.2). After combining data on cases in vaccine recipients and contacts, the effect of DTP injections on the risk of paralysis was elevated but

Table 3. Effect of the Timing of Intramuscular Injections in Relation to the Receipt of OPV among Vaccine Recipients with Paralytic Poliomyelitis and Their Matched Controls.*

TIMING OF INJECTIONS	CASES (N = 18)	CONTROLS (N = 90)	MATCHED ODDS RATIO (95% CI)
	no. (%)		
Before OPV (yes vs. no)	5 (28)	16 (18)	2.0 (0.6–7.1)
Simultaneous DTP injection (yes vs. no)	13 (72)	51 (57)	3.4 (0.7–17.1)
After OPV (yes vs. no)	9 (50)	2 (2)	56.7 (8.9–∞)†
Any injection (yes vs. no)	18 (100)	59 (66)	17.0 (2.5–∞)†

*Only injections given 0 to 30 days before the onset of paralysis are included. CI denotes confidence interval. Odds ratios were adjusted for matched sets by conditional logistic regression.

†The odds ratio and confidence interval were calculated by exact conditional logistic regression.

Table 4. Effect of the Timing of Intramuscular Injections, According to Weekly Intervals before the Onset of Paralysis, among Vaccine Recipients with Paralytic Poliomyelitis and Children with Contact Cases and Their Matched Controls.*

TIMING OF INJECTIONS BEFORE PARALYSIS	RECIPIENTS			CONTACTS		
	CASES (N = 18)	CONTROLS (N = 90)	MATCHED ODDS RATIO (95% CI)	CASES (N = 13)	CONTROLS (N = 61)	MATCHED ODDS RATIO (95% CI)
	no. (%)			no. (%)		
0–7 Days (any vs. none)	8 (44)	1 (1)	40.0 (5.0–319.8)	1 (8)	3 (5)	1.7 (0.2–16.0)
8–14 Days (any vs. none)	4 (22)	14 (16)	1.7 (0.4–7.0)	7 (54)	5 (8)	23.9 (2.9–198.8)
15–21 Days (any vs. none)	10 (56)	26 (29)	3.8 (1.2–12.3)	7 (54)	5 (8)	10.0 (2.5–39.2)
22–30 Days (any vs. none)	7 (39)	26 (29)	1.9 (0.5–6.4)	5 (38)	11 (18)	5.7 (1.0–33.3)
Any injection (any vs. none)	18 (100)	59 (66)	17.0 (2.5–∞)†	9 (69)	18 (30)	18.1 (2.1–155.2)

*Odds ratios were adjusted for matched sets by conditional logistic regression. CI denotes confidence interval.

†The odds ratio and confidence interval were calculated by exact conditional logistic regression.

did not achieve statistical significance (matched odds ratio, 3.1; 95 percent confidence interval, 0.9 to 10.8).

Population Attributable Risk

The population attributable risk for any intramuscular injection given within 30 days before the onset of paralysis in the children with poliomyelitis was 86 percent (95 percent confidence interval, 66 to 95 percent). Assuming a population attributable risk of 86 percent, the average annual number of vaccine-associated cases of paralytic poliomyelitis in Romania might have been reduced from 10.3 (the annual average from 1984 through 1992) to 1.4 if all intramuscular injections in young children within 30 days after exposure to OPV had been eliminated. The overall risk of vaccine-associated poliomyelitis in Romania would then be 1 case per 1.3 million doses of OPV distributed rather than the current risk of approximately 1 case per 178,000 doses.

DISCUSSION

It is common practice in Romania to prescribe antibiotics, given in multiple intramuscular injections, for febrile illnesses in infants. The strong associations we observed among antecedent illnesses, intramuscular injections, and an increased risk of vaccine-associated poliomyelitis may reflect three different causal mechanisms. First, among the 10 children with vaccine-associated poliomyelitis who had biphasic illness, the injections may have been a consequence of the minor illness and unrelated to paralytic disease. This mechanism, however, does not explain the significant association between intramuscular injections and the risk of paralysis among the 21 children with paralysis who had no preceding minor illness. Second, an antecedent illness (such as pneumonia), other than the early phase of poliomyelitis, may have increased the risk of vaccine-associated poliomyelitis independently of the number of intramuscular injections administered. If this mechanism applied, comparing children with poliomyelitis who had an antecedent illness with controls who had an anteced-

ent illness should have eliminated the effect of intramuscular injections on the risk of paralysis. On the contrary, however, a statistically significant association persisted. These observations suggest a third mechanism: intramuscular antibiotics given as therapy for an intercurrent illness in a child shortly after exposure to OPV may have precipitated paralytic disease.

Several additional lines of evidence suggest that intramuscular injections may be causally related to vaccine-associated paralytic poliomyelitis in Romanian children. The strength of the association between intramuscular injections and vaccine-associated paralysis was similar for the vaccine recipients and the

children who acquired the disease by contact, as was the dose–response effect. For cases in vaccine recipients, the timing of intramuscular injections with respect to the receipt of OPV was critical; injections administered after the receipt of OPV, but not before or at the same time as OPV, were associated with elevated risk. In addition, our findings are similar to observations in the late 1940s and 1950s that intramuscular injections have a tendency to “provoke” paralysis in the injected limbs of persons infected with wild-type poliovirus.^{21–24} This association was particularly noticeable in the United Kingdom, where DTP was injected into the arm and there was a reversal in the ratio of arm involvement to leg involvement among children with paralytic poliomyelitis.²⁵ Subsequent studies confirmed that intramuscular injections increased the risk of paralytic poliomyelitis. A single intramuscular injection given during the incubation period of wild-type poliovirus infection doubled the risk of paralysis, and multiple injections increased the risk more than 10-fold.^{6,8,26–28}

The dose–response effect seen in wild-type poliovirus infection is mirrored in our study of children infected by the vaccine virus. The provoking effect of injections in persons with wild-type poliovirus infection has typically been observed 0 to 7 days (in some studies, 0 to 2 days) and 8 to 21 days before the onset of paralysis.^{6,8,21,25–27,29} In our study, the periods of greatest risk associated with injections were similar. Studies conducted during outbreaks of wild-type poliovirus infection have found a provoking effect of a variety of substances injected intramuscularly (including penicillin, DTP, quinine, and mercurial compounds). In addition, studies in monkeys demonstrated that the trauma of an intramuscular needle puncture (without the injection of any substance) was associated with an increased risk of paralysis in the injected limb.³⁰ In our study, the higher risk associated with the intramuscular injection of antibiotics, as compared with DTP, appears to be due to the number and timing of injections rather than to the substance injected. The consistency of these obser-

vations, together with the biologic plausibility of the mechanism based on experience with wild-type poliovirus, strongly suggests a causal association between intramuscular injections and vaccine-associated paralytic poliomyelitis.

Aside from isolated case reports,^{31,32} no previous association between intramuscular injections given within 30 days before the onset of paralysis and an increased risk of vaccine-associated paralytic poliomyelitis has been reported in the medical literature. If this association is causal, why has it not been detected before? The reason may be that, in most places, intramuscular injections are relatively infrequent during the first year of life and are seldom given during the incubation period of OPV. In Romania, however, the widespread use of antibiotics to treat acute febrile illness and the lack of oral antibiotic preparations result in numerous intramuscular injections during the first six months of life,³³ when the first dose of OPV is given. This practice, combined with comprehensive surveillance for poliomyelitis, may have facilitated the detection of the increased risk of vaccine-associated paralysis.

The matched odds ratios for the administration of DTP — either simultaneously with OPV in the vaccine recipients or during the 30 days before the onset of paralysis in the children with contact cases — were elevated, but the increases were not statistically significant and were substantially lower than those for penicillin and other antibiotics. The proved benefits of DTP and the logistic advantage of the simultaneous administration of OPV and other injected vaccines override any theoretical concern about the possible provocation of vaccine-associated poliomyelitis by DTP vaccine.

The pathogenesis of provocation paralysis is unknown. Two mechanisms have been postulated. First, local injury at the site of an intramuscular injection may allow virus to gain entry to peripheral nerve endings and then travel, by retrograde axonal transport, to the anterior horn, where replication results in cell destruction.^{34,35} Axonal transport of polioviruses has been demonstrated in monkeys³⁶ and transgenic mice.³⁴ Second, intramuscular injections may enhance the replication of poliovirus already in the central nervous system. Simoes and coworkers recently observed that Bonnet monkeys injected with Sabin virus type 1 in the ulnar nerve had mild neuronal damage and mild inflammation of the spinal cord.³⁷ When simultaneous intramuscular injections were given, viral replication was greatly increased, resulting in neuronal lysis and neuronophagia similar to that seen in cases caused by wild-type poliovirus. If these experimental findings pertain to humans, they suggest that multiple intramuscular injections given over a period of days may both facilitate the entry of the poliovirus in the vaccine into the central nervous system and increase viral replication in anterior horn cells, thus transforming what would have been asymptomatic infection into paralytic disease.

The small numbers of cases and retrospective data collection were important limitations of our study. To

increase its statistical power, we selected up to five controls per case. To avoid recall bias, we counted intramuscular injections only if they were documented in the medical records. The site of injection was not routinely recorded, a fact that limited our ability to analyze the risk of vaccine-associated poliomyelitis in a limb according to the number of injections received in that limb. Although the patients with vaccine-associated poliomyelitis were not tested, undiagnosed HIV infection is unlikely to have placed them at higher risk of vaccine-associated paralysis, because one to four years after acute poliomyelitis none of the case children have been given a diagnosis of HIV infection and none have died.

In Romania, as well as other countries where intramuscular injections are a popular means of administering medications to young children,³⁸ a concerted effort will be required to decrease reliance on injectable preparations. The high population attributable risk for any intramuscular injection given within 30 days before the onset of paralysis suggests that the replacement of intramuscular antibiotics for use in infants with either oral or intravenous preparations may reduce the risk of vaccine-associated poliomyelitis in Romania to a level similar to that in other countries.^{4,39,40}

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