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Adverse Reactions to Cholera Vaccine– Taipei City and Miaoli County

In May 1985, two clusters of adverse reactions to cholera vaccine were reported to the Bureau of Disease Control. The vaccine associated with both clusters (agar grown fluid type containing 8×10^9 total vibrios per ml of Inaba and Ogawa serotypes) was manufactured in Taiwan by the National Institute of Preventive Medicine.

The first cluster of reactions occurred among a group of 945 Taipei City Bank employees who received 1 ml of cholera vaccine (lot #73-2) during an employee immunization program. Approximately 20 employees initially reported mild to moderate local reactions (pain, induration, and erythema). Questionnaires were distributed to all vaccinees to identify the number with adverse reactions, their signs and symptoms, and potential risk factors. A total of 631 questionnaires were returned for a response rate of 67 percent. Thirty-five (5.5%) employees reported adverse reactions including tenderness (80%), swelling at the injection site (69%), induration (60%), malaise (29%), erythema (17%), fever (17%), and lymphadenopathy (9%). Onset of reactions occurred 1-8 days (median = 5.3 days) after injection. There was no association of reactions with time or day of immunization, or by worksite. No differences were noted between reactors and nonreactors with respect to age or sex. Risk factors for reactions included a history of previous reaction to cholera vaccine ($p=3.66\times10^{-3}$, Fisher's exact test), and illness in the week preceding vaccination ($p=3.49\times10^{-3}$, FET). Previous immunization with cholera vaccine was not associated with reactions.

The second cluster of reactions was reported among primary school children in Miaoli County after cholera vaccine (lot #73-6) was administered to school

children during a county-wide mass immunization campaign. Although all 161 schools in Miaoli County participated in the campaign, reports of vaccine reactions were received from only two elementary schools: one in the township of Ta Hu (enrollment 905) and the other in Kong Kwan (enrollment 536). Two different methods were used to administer cholera vaccine in Miaoli County: students in larger schools (>500 students) were vaccinated with a pneumatic jet injector gun (Hyjector YS-2, Tokyo Sokuhan Company) and students in smaller schools were vaccinated with disposable needles and syringes.

To determine rates and type of reaction to cholera vaccine, questionnaires were sent to parents of all children in the larger of the two elementary schools reporting reactions (school A). Students in school A received cholera vaccine via jet injector gun. For comparison, questionnaires were also sent to parents of a nearby elementary school (school B) in which students received vaccine via needle and syringe. No spontaneous reports of vaccine reactions had been received from school B. In school A, 776 questionnaires were returned by 868 vaccinees for a response rate of 89 percent. In school B, 327 questionnaires were returned by 335 vaccinees for a response rate of 98 percent. A probable reaction to cholera vaccine was defined as any local or systemic sign or symptom noted after the administration of cholera vaccine. The rate of reactions in schools A and B were 29 and 19 percent, respectively ($p<0.002$). Signs and symptoms were similar among students in both schools (Table 1). The median time from injection to onset of symptoms was two hours for students in school A and five hours for students in school B ($p>0.05$; Wilcoxon rank sum test). The median duration of symptoms was four hours for students in both schools. Reaction rates did not differ significantly by school grade, however, there was significant clustering of reactions in classrooms of both schools: $p<0.001$ for schools A and B (x^2 goodness-of-fit). The pattern of clustering was unrelated to time of vaccination, personnel administering the vaccine, or individual vials of vaccine from the same lot number.

To identify potential risk factors for vaccine reaction, we redefined a reaction

Table 1 Comparison of signs and symptoms among students with reaction to cholera vaccine in schools A and B.

Signs and Symptoms	School A (N=223)	School B (N=63)
Dizziness	59%	35%
Fever	48%	51%
Headache	46%	24%
Nausea	19%	13%
Chills	10%	11%
Vomiting	5%	5%
Rash	4%	11%
Cyanosis	2%	6%

more strictly as a student with fever >39°C, or ≥38°C plus two or more symptoms including nausea, vomiting, headache, dizziness, chills, localized erythema or induration. Two factors were significantly associated with reactions in both schools: previous history of a reaction to cholera vaccine (school A, $p<10^{-5}$; school B, $p=1.49\times10^{-8}$, FET) and illness during the week preceding vaccination (school A, $p<0.01$; school B, $p=9.19\times10^{-3}$, FET). Once the effects of these two factors were taken into account, the clustering of reactions in classrooms was no longer significant in either school (Mantel-Haenszel $x^2=1.52$ for school A and 2.90 for school B).

Vaccine vials associated with reactions were tested by the laboratory of the Food and Drug Bureau. The vaccines met quality control standards for sterility, pH, nitrogen and phenol content. The production records of all lots of cholera vaccine manufactured in 1984, including the two lots associated with reactions, were reviewed and all had passed sterility, abnormal toxicity, and safety tests.

The reactions among bank employees differed significantly from those among primary school children. Age may have an important influence on type of reaction to cholera vaccine, however, we were unable to show any age-specific differences in reaction rates or type of reactions within the age groups of our study. Alternatively, there could be an undetected chemical or biologic difference between the two different vaccine lots which could account for differences in the characteristics of reactions.

In both bank employees and school children, a history of previous reaction to cholera vaccine and illness in the week preceding vaccination were significantly associated with reactions. Previous reaction may indicate a hypersensitivity to some component of cholera vaccine which predisposes to subsequent reactions. Preceding illness could also alter the immune system permitting increased susceptibility to reactions from vaccines.

The difference in rates of reaction between students vaccinated by jet injector gun and needle and syringe are difficult to assess since only two schools were studied. Controlling for previous reaction to cholera vaccine and illness in the week preceding vaccination did not eliminate the significant differences in reaction rates between the two schools (Mantel-Haenszel $x^2=24.73$, $p<10^{-6}$). It is possible that the injector gun produced more local trauma predisposing to higher rates of reaction, although this cannot be proved with the data presently available.

Reported by Taipei City Health Department; Miaoli County Health Bureau; National Institute of Preventive Medicine; Food and Drug Bureau; Bureau of Disease Control, Department of Health, Executive Yuan.

Editorial note: Mild to moderate reactions to cholera vaccine are common, however, specific data on rates and type of reactions are limited. In a field trial of high potency cholera vaccine in Indonesia in 1973-1975, local reactions (pain, erythema, swelling and induration) occurred in 30-40 percent of children 1-9 years of age, and systemic reactions (headache, malaise) occurred in 4-8 percent[1]. Since the vaccine used in the Indonesia field trial contained twice the number of organisms