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A second controlled field trial of a serogroup A meningococcal polysaccharide vaccine in Alexandria

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The encouraging results of an earlier controlled field trial of the serogroup A meningococcal polysaccharide vaccine in the prevention of clinical disease prompted this study, the aim of which was to evaluate further the effectiveness of another lot of this type of vaccine, the duration of immunity, and the effectiveness against meningococcal carriage. A controlled field trial was carried out in early 1973 on 176 646 schoolchildren 6–15 years of age, of whom half received the serogroup A polysaccharide vaccine and the other half tetanus toxoid as a control. The incidence of cerebrospinal meningitis caused by serogroup A meningococci was 89% lower in the immunized group than in the controls for one year only. With regard to its effect on carriage, the vaccine was found to reduce to less than half the rate of new acquisition of serogroup A meningococci during the period immediately following immunization. The duration of the carrier state was also shortened in the immunized group.

Many attempts have been made since the early years of this century to prepare an efficient vaccine against cerebrospinal meningitis (CSM). For the most part, these vaccines were whole-cell, killed vaccines. Some of them produced severe reactions, most had little protective effect, and none satisfied the requirements of a good vaccine (*1*). Recently, serogroup C and then serogroup A polysaccharide vaccines have been produced in a form suitable for injection into human beings (*2*). These vaccines have been proved to produce good serological response and to prevent homologous meningococcal disease (*3-7*).

The first controlled field trial to test the efficiency of a serogroup A polysaccharide vaccine in preventing clinical illness was carried out in Egypt. The results of the follow-up of the vaccinees during the period of the trial (1971–72) showed that the vaccine conferred significant protection: 8 cases were reported among the controls and none among the vaccinees (*6*). During the next two seasons (1972–73 and 1973–74), 7 cases were discovered, all of which were in the control group. Four of these cases occurred during the 1972–73 season and the other 3 during the 1973–74 season. The total number of cases was 15, all of which occurred in the control group. This indicated that the vaccine produced a high degree of immunity for at least three years.

In view of the encouraging results obtained in this trial, it was decided to immunize more students with the serogroup A meningococcal polysaccharide vaccine in a controlled clinical trial aimed at obtaining further data on the effectiveness of the vaccine in preventing meningococcal disease and the duration of immunity gained through immunization. A further objective was to test the effectiveness of the vaccine against meningococcal carriage.

MATERIALS AND METHODS

Plan of the study

The study was conducted as a controlled field trial following essentially the same procedures as those used in the first trial (*6*). It was conducted on

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Table 1. Distribution of vaccinees by age, sex, and type of vaccine

Age (years)	Meningococcal vaccine		Tetanus toxoid		Total	
	Male	Female	Male	Female	Male	Female
6	6 334	5 587	6 282	5 631	12 616	11 218
7	6 199	5 553	6 209	5 585	12 408	11 138
8	6 157	5 635	6 127	5 607	12 284	11 242
9	7 457	6 513	7 472	6 582	14 929	13 095
10	5 912	5 436	5 952	5 469	11 864	10 905
11	4 724	4 275	4 749	4 227	9 473	8 502
12	2 988	2 573	2 952	2 615	5 940	5 188
13	3 304	2 785	3 334	2 796	6 638	5 581
⩾ 14	3 806	3 025	3 749	3 045	7 555	6 070
Total	46 881	41 382	46 826	41 557	93 707	82 939

Alexandrian schoolchildren 6–15 years of age who had not been included in the first trial. All schools in Alexandria where immunization had not previously been performed were included in the study. The education and school health authorities of Alexandria, the Ministry of Health, the United States Naval Medical Research Unit No. 3, and the local political organization were represented on the committee that was responsible for the conduct of the trial. The aim of the study was made known and explained to the population. The schools asked the parents for approval to immunize their children against CSM or tetanus and, with very few exceptions, all parents agreed. Only those children whose parents approved were immunized.

The population was divided by systematic random allocation of school classes of each grade into two groups, a CSM vaccine group and a control group. The vaccine group received serogroup A meningococcal polysaccharide vaccine and the control group received tetanus toxoid. The vaccines were coded and their identity was not disclosed to those involved in the trial until after its completion.

Study population

Of the 193 827 schoolchildren 6–15 years of age enrolled in the selected schools, a total of 176 646 (91.1%) were immunized. The rest were mostly absent from school on the day of immunization.

The vaccinees comprised 88 263 who received the serogroup A polysaccharide vaccine and 88 383 who received the tetanus toxoid. The distribution of the vaccinees by age, sex, and type of vaccine is presented in Table 1. Comparing the two groups of vaccinees, no significant difference is observed either in age or in sex. By virtue of the allocation of alternate classes within the same school to meningococcal vaccine and tetanus toxoid, it can safely be stated that the two groups were from similar socioeconomic backgrounds. The medical facilities were also the same for the two groups.

Vaccine and immunization procedures

The serogroup A meningococcal polysaccharide vaccine was prepared as described by Gotschlich et al. (*2*, *8*) and in accordance with WHO requirements. The administered dose was 50 μg contained in 0.5 ml of diluent. The tetanus toxoid dose was also 0.5 ml. Both vaccines were of similar appearance. They were transported in dry form and were stored at or below —20°C before reconstitution and use. Samples of the vaccine were obtained before shipment, upon arrival in Egypt, and following completion of the trial, and were tested for degradation as shown by reduction in the polysaccharide molecular weight. The results showed no detectable degradation of the vaccine during the period of immunization.

Immunizations were performed by teams of physicians and nurses using hypodermic jet injectors. The amount of vaccine estimated to be needed for daily use was withdrawn from storage and reconstituted at the vaccination site as required.

The two vaccines were given to alternate classes within each school grade, all students in one class receiving one vaccine while all those in the next class received the other. This procedure was felt to be the

most appropriate for achieving immunization efficiency with the large numbers involved. In view of the fact that students were not selectively assigned to classes, the application of this procedure was not felt to introduce any bias between the two groups of vaccinees.

The vaccine was administered during the period from 27 January to 12 February 1973 in 12 working days, to an average of about 15 000 vaccinees per day.

Follow-up and assessment of results

Assessment of the efficacy of the meningococcal vaccine in preventing CSM was carried out by comparing the incidence of the disease in the study group that received the vaccine with the incidence in the control group. Each suspected case was immediately transferred to the Alexandria Communicable Diseases Hospital for diagnosis and treatment. The school health authorities were asked to report all absences of more than 3 days in succession and any deaths. These were investigated through home visiting to exclude the possibility that they might be suspected cases of CSM. On admission to hospital of any patient 5–17 years old, whether he had been referred by the school health department or by another health service facility or a private physician, the patient's identity and the school attended were determined. These were confirmed with the school authorities and checked against the data on the serially-numbered card that had been prepared for each child at the time of immunization. During the second year of follow-up, the school attended by the patient at the time of immunization, i.e., in the previous year, was recorded.

Diagnosis was based on the isolation of meningococci from the cerebrospinal fluid (CSF) or, when this was not possible, on either the detection of meningococcal antigens in the CSF by the immunoosmophoresis (IOP) test or the demonstration of a significant rise in antibody titre in acute or convalescent sera. As far as possible, the three tests were carried out on all suspected cases and those positive for one or more of them were considered to be proven cases.

The attack rates among the vaccinees and the controls were calculated for the three seasons and the significance of the difference was tested by the ZI test (*10*).

Assessment of the efficacy of the vaccine against meningococcal carriage was carried out on two populations. The first was a group of 510 students comprising 256 vaccinees and 254 controls. Their meningococcal carriage status was identified prior to their immunization by means of three carrier surveys during one week, with a two-day interval between each survey. They were then followed up at carrier surveys at 4-week intervals.

The second group studied for carriage consisted of the class contacts of cases of meningitis. These were examined for carriage one week after the last contact with a case of meningococcal meningitis. This group totalled 841 students during the two seasons 1973–74 and 1974–75.

RESULTS

Morbidity

During the two years of follow-up, 16 cases of serogroup A meningococcal meningitis occurred in the vaccine study population. They comprised 4 cases in the group that received the meningococcal vaccine and 12 in the control group that received tetanus toxoid. The difference in the case rates between the vaccinees and the controls was found to be statistically significant ($P = < 0.01$). Table 2 presents the basic data on the 16 cases.

It appears from the table that there was a difference between the number of cases among the vaccinees and the controls during the first 12 months from the date of immunization, when all but 1 of 10 identified cases were in the control group. After this period, the cases were equally divided between the vaccinees and the controls, with 3 cases in each group.

The attack rate in the first year was 1.13 per 100 000 in the immunized and 10.20 per 100 000 in the nonimmunized group, representing a decrease of incidence of 88.9% in the immunized group. In the second year of follow-up, the corresponding rates were 3.39 and 3.40, respectively.

The occurrence of cases of serogroup A meningococcal meningitis during the two years of study among students who had not been included in either the first or the second trial was investigated. During the first year of follow-up, 16 cases of serogroup A meningococcal meningitis were identified among the 210 659 nonimmunized students (contrast group), giving a rate of 7.60 per 100 000. In the second year of follow-up, the number of students in the contrast group was 260 473 and 10 cases of serogroup A meningococcal meningitis were identified among them, giving a rate of 3.84 per 100 000. The rates in the contrast group were not significantly different from those in the control group in the corresponding years. However, the case rate in this group was

Table 2. Serogroup A meningococcal meningitis cases among immunized students

Immunization		Patient		Period between immunization & onset (months)	Diagnostic criteria [a]			
Type	Date (1973)	Age (years)	Sex		Culture	IOP	Acute HA titre	Convalescent HA titre
control	31/1	9	M	Under 1	+	+	n.d.	1/16
control	1/2	8	M	1	+	+	1/4	1/8
control	8/2	11	F	1	+	n.d.	negative	1/16
control	28/1	11	F	1	+	n.d.	negative	1/16
control	8/2	15	M	2	+	+	1/8	1/64
control	29/1	6	F	2	−	n.d.	negative	1/16
group A	5/2	8	F	4	−	+	1/8	1/16
control	29/1	8	F	10	+	n.d.	n.d.	n.d.
control	28/1	13	F	11	+	n.d.	1/8	1/8
control	26/1	12	F	12	+	n.d.	1/4	1/8
Total (1st year) : 9 controls & 1 Group A								
control	1/2	11	F	13	+	n.d.	1/8	1/16
group A	30/1	13	M	17	+	+	1/4	1/16
group A	8/2	9	F	17	+	+	1/8	1/32
control	6/2	8	M	18	N.g.	+	negative	1/8
group A	31/1	10	M	19	−	n.d.	1/4	1/16
control	29/1	7	F	20	−	+	negative	1/32
Total (2nd year) : 3 controls & 3 group A								

[a] IOP = immuno-osmophoresis; n.d. = not done; N.g. = *Neisseria gonorrhoeae* meningitis.

significantly higher than in the serogroup A vaccine group only in the first year of follow-up.

All patients showed typical clinical signs and symptoms of CSM, and after receiving treatment they all recovered. In 11 cases, it was possible to isolate serogroup A meningococci from the CSF. In 1 of the remaining 5 cases nontypable meningococci were isolated and in the other 4 cases the CSF culture was negative. The serogroup A meningococcal antigen was specifically detected and identified in the CSF by the IOP test in all the 8 patients whose CSF was tested by this method. Serological testing of the blood samples obtained on admission and after 10 days by the haemagglutination test showed positive results (a 4-fold or more increase in titre) in 10 cases and was the only diagnostic criterion in 2 cases.

Carriage

The data obtained from the carrier surveys carried out on the immunized children at 4-week intervals were studied to detect new acquisitions of serogroup A meningococci and to determine the duration of the carrier state. The new acquisition rates were calculated by student-month of follow-up, since the numbers of the study population varied during the period of follow-up.

Table 3 shows that during the first period of follow-up (the 3 months following immunization), the new acquisition rate among the vaccinees was less than half that among the controls (4.9 and 12.0 per 1000 student-months of follow-up, respectively). The new acquisition rates during the 6-month period beginning 9 months after immunization were 10.4 and 13.6 per 1000 student-months of follow-up for the vaccinees and the controls, respectively. During the 6-month period beginning 21 months after immunization, no significant difference was observed in the rates of new acquisitions between the vaccinees and the controls (10.4 and 10.0 per 1000 student-months of follow-up, respectively).

Table 3. New acquisitions of serogroup A meningococci in relation to immunization

Period of follow-up	New acquisitions of serogroup A meningococci	Immunized	Controls
February 1973 to April 1973	No. of new acquisitions	5	12
	No. of student-months of follow-up	1021	1003
	Rate/1000 student-months of follow-up	4.9	12.0
October 1973 to April 1974	No. of new acquisitions	16	20
	No. of student-months of follow-up	1539	1476
	Rate/1000 student-months of follow-up	10.4	13.6
October 1974 to March 1975	No. of new acquisitions	14	13
	No. of student-months of follow-up	1341	1301
	Rate/1000 student-months of follow-up	10.4	10.0

Table 4. Duration of carriage of serogroup A meningococci by immunization status

Period	Duration of carriage	Immunized		Controls	
		No.	%	No.	%
February 1973 to April 1974	Less than 4 weeks	18	86	15	47
	4 weeks or more	3	14	17	53
	Total	21	100	32	100
October 1974 to March 1975	Less than 4 weeks	12	86	8	62
	4 weeks or more	2	14	5	38
	Total	14	100	13	100

Table 5. Serogroup A meningococcal carriage among contacts of cases according to their immunization status

Period	Serogroup A meningococcal carriage	Immunized	Controls
October 1973 to May 1974	No. of carriers	8	48
	No. of contacts examined	193	378
	Carrier rate/100	4.1	12.7
October 1974 to March 1975	No. of carriers	18	10
	No. of contacts examined	178	92
	Carrier rate/100	10.1	10.9

In estimating the duration of carriage, we adopted the assumption of Greenfield et al. (*11*) that an individual with a negative swab bracketed by cultures positive for the same serogroup should be labelled as a carrier of that serogroup. Table 4 shows that the duration of carriage was much shorter among the vaccinees than among the controls throughout the period of follow-up.

For the two periods of follow-up, 5 out of 35 (14%) of the vaccinees who acquired serogroup A meningococci remained carriers for 4 weeks or more during the period of follow-up, as compared with 22 out of 45 (49%) of the controls.

The occurrence of serogroup A meningococcal carriers among school contacts of cases of serogroup A meningococcal meningitis identified in the study population is shown in Table 5. During the period October 1973–May 1974 (8–15 months following immunization), the serogroup A meningococcal carrier rate among the vaccinees was about one-third of that among the controls (4.15% and 12.7%, respectively). On the other hand, during the period October 1974–March 1975 practically no difference was observed between the carrier rates in the two groups (10.1% and 10.9% among vaccinees and controls, respectively).

DISCUSSION

The results of this field trial indicate that the serogroup A meningococcal polysaccharide vaccine under study reduced the occurrence of CSM caused by serogroup A meningococci to significantly low levels during the first year following immunization. In subsequent months immunization seemed to have no effect on the attack rates.

The vaccine used in this study was of the same lot (V-7) (*9, 12*) as that used in a controlled field trial in Sudan (*7*) where high efficacy during the first epidemic season was also found. The results of these two studies are therefore consistent. The failure of this vaccine to prevent the disease after the first year is not consistent with the long duration of immunity observed in our first field trial with serogroup A polysaccharide vaccine of another lot (V-6) (*12*). Vaccine lot V-6, which was shown to give protection for at least three years, had a molecular weight of about 170 000 (*6*), whereas the present lot (V-7) had a molecular weight of about 75 000 (7). It is probable that the molecular weight has an effect on both the degree and the duration of immunity.

During the first year of follow-up the vaccine was found to reduce significantly the rate of new acquisitions of nasopharyngeal carriage of serogroup A meningococci, the effect being specific for that serogroup. There was also a significant reduction in the duration of carriage of serogroup A meningococci among the vaccinees. This indicates that chronicity of colonization was less frequent among those immunized with serogroup A vaccine, as observed also by Gotschlich et al. (*13*).

To conclude, it would appear that serogroup A meningococcal polysaccharide vaccine has a much more dramatic effect on disease prevention than on control of the carrier state. This observation has a bearing on the application of the vaccine in public health practice and on the selection of a strategy for cerebrospinal meningitis control.

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RÉSUMÉ

DEUXIÈME ESSAI CONTRÔLÉ SUR LE TERRAIN A ALEXANDRIE D'UN VACCIN POLYSACCHARIDIQUE CONTRE LES MÉNINGOCOQUES DU SÉROGROUPE A

Cette étude a été suscitée par les résultats encourageants d'un premier essai contrôlé sur le terrain du vaccin polysaccharidique contre les méningocoques du sérogroupe A pour prévenir l'atteinte clinique. Il s'agissait de procéder à une nouvelle évaluation portant sur un autre lot du même type de vaccin et intéressant son efficacité à l'égard des cas cliniques et à l'égard des porteurs, ainsi que la durée de l'immunité conférée. Dans ce nouvel essai ont été englobés 176 646 écoliers de 6 à 15 ans, dont la moitié ont reçu le vaccin polysaccharidique du sérogroupe A et l'autre moitié de l'anatoxine tétanique en tant que groupe témoin. L'incidence de la méningite cérébro-spinale due à des méningocoques du sérogroupe A a été de 89% plus faible dans le groupe vacciné que dans le groupe témoin pendant une année seulement. En ce qui concerne l'effet sur les porteurs, il a été établi que le vaccin réduisait le taux d'acquisition de méningocoques du sérogroupe A de plus de moitié durant la période suivant immédiatement la vaccination. On a aussi constaté que l'état de porteur persistait moins longtemps dans le groupe vacciné.

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