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Epidemiological investigation of an outbreak of meningococcal meningitis in Makkah (Mecca), Saudi Arabia, 1992

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SUMMARY

During March and April of 1992, the health surveillance system began detecting increasing numbers of cases of meningococcal disease (MCD) in the Islamic holy city of Makkah (Mecca). We identified 102 bacteriologically confirmed cases (CC) and 80 suspected cases (SC) of MCD. *Neisseria meningitidis* was identified as Group A, III-1 clone. The ratio of male:female cases was 2·9:1. All age groups of males were affected. There was only one case among women aged 10–30; 50% of the adult female cases were 55 or older. The case-fatality ratio (CFR) was 14·7% among CC. Pakistanis, who comprised about one-third of the CC, had a CFR of 26·7%. Fifty-nine percent of CC were religious visitors. CC in residents were most common in persons living near the Holy Mosque (Haram), where the carriage rate reached 86%. A mass vaccination program against MCD was instituted, using AC bivalent meningococcal vaccine (MCV). An abrupt drop, from a mean of 15 CC per week to 2 CC per week (only in visitors), coincided with vaccinating 600000 persons over 2 weeks. Makkah residents who had been vaccinated against MCD were less likely to have contracted MCD (OR = 0·17, 95% CI: 0·06–0·50). MCV was of no significant protective value if it had been administered 5 years before the outbreak. The main reason for not being vaccinated as stated by both cases (71%) and controls (45%) was not knowing about the disease. The age and sex differences probably relate to differences in exposures to crowded conditions. Health education should illuminate the seriousness of the disease and the importance of vaccination.

INTRODUCTION

The annual Islamic pilgrimage to Makkah (Mecca), which attracts pilgrims from almost every country, plays a central role in the amplification and dissemination of meningococcal disease (MCD) all over the world. In 1987, *Neisseria meningitidis* group A (clone III-1), previously identified in Nepal, China and Europe, spread

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among pilgrims [1]. Pilgrims who became meningococcal carriers during their stay in Makkah further disseminated this strain to both developing and developed countries around the world on their return home [1–5]. In 1987 there were 1841 confirmed cases of MCD reported in Saudi Arabia, predominantly in three cities (Makkah, Madinah and Jeddah) most closely associated with pilgrimage [6, 7]. In 1988 there was a smaller outbreak of 305 confirmed cases [8]. Pilgrimage-associated outbreaks of MCD also occurred in earlier years, but were less well documented.

There are two types of pilgrimage. Umra may be performed at any time during the year, although pilgrims from outside Saudi Arabia can get Umra visas only for the lunar months 1–9 (Muharram to Ramadan). Umra visits reach their peak during Ramadan, the Islamic fasting month. During the 10th and 11th lunar months pilgrims begin arriving in preparation for Hajj, the 'major' pilgrimage. Although the Hajj rituals themselves last only from the 9th to the 12th day of the 12th lunar month (Dhul Hijja), pilgrims from outside Saudi Arabia must have Hajj visas if they come any time from the 10th to the 12th month.

All previous MCD outbreaks had occurred after Ramadan (ie., toward the end of Shawal, the 10th lunar month) through the Hajj. Until 1987 Saudi Arabia required vaccination against meningococcal meningitis (MCV) for Hajj visas only for pilgrims from sub-Saharan African countries. In that year, high MCD attack rates in pilgrims from other countries prompted authorities to extend the MCV requirement to all Hajj visas from all countries. Beginning in 1988, all Hajj visitors were required to produce a certificate of vaccination against MCD issued not more than 3 years and not less than 10 days before arrival in Saudi Arabia. Pilgrims from countries where MCD is endemic could be examined, suspect MCD cases would be isolated and contacts put under observation [9].

In addition, residents of Hajj-related areas and Hajj pilgrims from Saudi Arabia were encouraged to receive MCV (provided free) and Hajj workers were vaccinated. In 1991, following the Gulf conflict, unprecedented numbers of pilgrims came for Umra. Accordingly, 2 months before Ramadan in 1992, the authorities extended the MCV requirement to all Umra visas.

Hajj visits are normally regimented and organized. The Saudi government works cooperatively with Hajj committees from all major Muslim countries to achieve a safe pilgrimage; among other preventive measures they ensure MCD vaccination. Hajj pilgrims normally come in groups, which may be more effectively vaccinated. However, some religious visitors may manage to get entry visas without being vaccinated. During the Hajj season, extra workers are at Jeddah airport to vaccinate groups or individuals suspected by the Saudi health authorities of being unvaccinated against MCD. Doctors, especially those working in the pilgrimage area, are reminded about MCD before every Hajj season [10]. In addition, MCD surveillance is strengthened, especially in the pilgrimage area. Daily reports of both suspected and bacteriologically confirmed cases from all hospitals are required.

Umra, in contrast, is an individual pilgrimage and does not fall under the close scrutiny of the Hajj authorities, although MCD surveillance is increased during Ramadan. During Ramadan of 1992, this surveillance detected an outbreak of MCD both in Makkah residents and among Umra visitors. In response, a mass

vaccination campaign using AC bivalent MCV was begun. This paper describes the epidemiological characteristics of the outbreak and documents successful control of an outbreak of MCD by mass vaccination.

MATERIALS AND METHODS

Background

The holy city of Makkah (Mecca) lies in western Saudi Arabia. Summer temperatures can reach 47·8 °C (mean daily high) and winter temperatures drop to 10·2 °C (mean daily low). Relative humidity is low (range between 10–92%, mean monthly range 36–61%) [11]. The resident population is about 800000; during Ramadan, the population (including Umra visitors) increases four- to fivefold. The city has 6 government hospitals, 2 private hospitals and 73 primary health care centres. Private hospitals always refer suspected cases of MCD to the nearest government hospital.

Health authorities in Makkah, especially prior to the annual pilgrimage season, provide MCV vaccinations to both residents and to religious visitors who for some reason were not vaccinated in their home countries. When the MCD outbreak was recognized in 1992, a mass vaccination programme against MCD was launched using mobile vaccination units. Target areas included the Holy Mosque (Haram), shopping centres, schools and residential areas. Vaccination units at hospitals and primary health care centres were reinforced.

During this mass vaccination campaign, more than 600000 people were vaccinated within 2 weeks. Concomitantly, more than one million people were vaccinated in Jeddah city, including all new religious visitors arriving at Jeddah seaport and/or international airport as well as other international ports. People throughout the Kingdom were encouraged to receive vaccination against MCD.

Case definitions

A suspected case (SC) of MCD was defined as any person who presented during the outbreak period (5 March 1992–15 June 1992) with sudden onset fever, headache and other sign of meningeal irritation, and turbid cerebrospinal fluid (CSF); if *N. meningitidis* was not isolated by culture or detected by latex agglutination (Wellcogen Bacterial Antigen Kit; latex test to detect *Streptococcus* group B, *H. influenzae* type b, *S. pneumoniae*, *N. meningitidis* ABCYW135 and *E. coli* KI antigens, Murex Diagnostics Limited), and no other diagnosis was established, the patient was treated empirically as a case of MCD. Lumbar puncture was performed on all SCs. However some SCs had this test done after initiation of treatment and not all CSF specimens were subjected to all laboratory tests. Blood culture was performed in 10 patients only (including 3 SCs). Cases of MCD were regarded as confirmed (CC) if *N. meningitidis* was isolated from a SC by culture from CSF and/or blood, or was detected by latex agglutination.

Methods

We reviewed medical records of admission, emergency, and infection control departments and laboratory logbooks for all MCD cases in the six government hospitals in Makkah. We interviewed all MCD (SC and CC) cases admitted to the

hospitals. In our interviews, we identified reasons why people had not been vaccinated against meningitis. We compared each CC in Makkah residents with 3 or 4 control persons of similar age and the same sex (but not necessarily the same nationality) from houses on the same block as the house of the case. If control persons of the same age and sex were not found on the same block, then we continued to the next block. All controls were Makkah residents.

To estimate the meningococcal carriage rate (not a main objective of the study), we took high throat swabs from a random sample of 42 apparently healthy adult males selected consecutively at one of the doors of the Haram after a congregational prayer on 7 May 1992; no questions were asked. Also, a set of paired swabs was taken from 116 Indonesian pilgrims who left Riyadh for Makkah in an organized group trip 2 months after the outbreak was over. They were predominantly females working as housemaids in Riyadh. Swabs were taken as the pilgrims left Riyadh on 7 June for Makkah and when they returned on 15 June 1992. Throat swabs were carried in Ames transport medium and were plated promptly. Eight lyophilized bacterial isolates from cases and carriers were sent to the Centers for Disease Control and Prevention (CDC) in Atlanta (USA) for eletrophoretic typing.

Data were analysed using Epi Info software (version 5.01b)[12]. The one-tailed t-test was used to test the difference between two means; a P-value of less than 0·05 was considered significant[13]. Vaccine efficacy (VE%) was calculted as (1-OR) × 100 where OR is the odds ratio[14].

RESULTS

During the outbreak period we detected 102 bacteriologically confirmed cases (CC) and 80 suspected cases (SC) of MCD. Clinical characteristics of SC and CC are shown in Table 1. The organism isolated from CC during Ramadan and from the Indonesian pilgrims during Hajj was identified by the CDC as *N. meningitidis*, group A, III-1 clone. Of the CC, *N. meningitidis* was isolated from the blood of seven patients. The overall case-fatality rate (CFR) for CC was 14·7% (15 of 102). The highest CFR (26·7%) was among pilgrims from Pakistan (8 of 30 CC). There were no fatal MCD cases among 16 Egyptian CC. The difference in CFR between Pakistani and Egyptian patients was statistically significant (P value $< 0{\cdot}0005$, test between two proportions). Other bacteria, *Streptococcus pneumoniae* (one from CSF and another from blood) and *Pasteurella multocida* (one from blood, data shown in Table 1), were identified from three additional patients admitted as SC. CC reported sooner to the hospitals, and they were hospitalized for longer periods than SC (Table 2).

The first CC of MCD was diagnosed mid-Ramadan (19 March 1992). Over the next 4 weeks, reported cases increased exponentially. After the mass vaccination campaign began during the second week of April, incident CC and SC numbers fell rapidly as the number of vaccinated people grew (Fig. 1). During May and June only two CC were detected per week. More than half (59%) of CC were religious visitors, whereas most of the SCs (56·3%) were residents of Makkah. Details of the numbers of religious visitors during Umra by country, age or sex were not available and attack rates cannot be presented. The distribution of CC of MCD by

Table 1. *Summary of clinical and laboratory profile of cases of MCD, Makkah, 1992*

Symptoms/clinical signs	% suspected cases ($N = 80$)	% confirmed cases ($N = 102$)
Fever	100	100
Neck stiffness	51·9	76·3
Headache	59·5	67·4
Kerning's sign	21·8	55·1
Vomiting	41·0	48·3
Coma	11·5	27·5
Petechial rash	6·4	23·3*
Convulsions	11·5	21·2
Joint pains	0·0	9·8
Nausea	2·6	7·3
Photophobia	0·0	4·8
Delirium	1·3	3·7
CSF gram stain		
Was positive	0	72·5
Was negative	73·8	16·7
Showed other bacteria	3·8†	0
Not done/not reported	22·6	10·8
CSF latex test for *Neisseria meningitidis* was		
Positive	0	72·5
Negative	67·5	9·8
Not done/unknown	32·5	17·6
Cerebrospinal fluid (CSF)	Suspected cases	Confirmed cases
CSF glucose < 40 mg/dl (N, %)	12/65 18·5%	71/102 69·6%
CSF WBC > 100 cells/μl (N, %)	11/27 40·7%	37/55 67·3%

* *Neisseria meningitidis* was detected by culture or swabs from skin lesions but not from CSF from 7 confirmed cases (6·9% of CC)

† Two isolates were *Streptococcus pneumoniae* (one from CSF and another from blood) and one isolate of *Pasteurella multocida* (from blood culture).

nationality is shown in Figure 2. There were 34 CC who were residents of Makkah. The distribution of the nationality of CC of Makkah residents and the control group is shown in Figure 3.

Among Makkah residents, 11 (32·3%) out of 34 CC and 4 (8·9%) out of 45 SC were females. The outbreak affected males in all age groups. However of all CC, there was only one female case aged between 10 and 30 years, and 50% of the cases in adult females occurred in women aged 55 years or more (Fig. 4). The majority of CC lived around the Haram.

The carriage rate was 86% around the Haram on 7 May 1992. *N. meningitidis* (clone III-1) was isolated from 2 of the 116 Indonesian pilgrims who had not been to Makkah during Ramadan. They had 6 days of exposure in Makkah. They were free from *N. meningitidis* when they left Riyadh for Makkah. *N. lactamica* was isolated from a third Indonesian pilgrim who accompanied the same group on her return from pilgrimage.

Twenty-four of 34 CC (70·1%) and 98 of 112 controls (87·5%) who were residents of Makkah were sure about their vaccination status. Table 3 shows the protective effect (OR and 95% CI) and the MCV efficacy. Those who were

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Table 2. *Social and demographic characteristics of cases of meningococcal meningitis (Makkah, 1992) and controls*

Characteristic	% suspected cases ($N = 80$)	% confirmed cases ($N = 102$)
Mean age (SD)	30·7 (19·5)	35·3 (21·1)
Residency status		
Makkah resident	56·3	33·3
Religious visitor	23·8	58·8
Undocumented	20·0	7·8

	Suspected cases		Confirmed cases		
	N	Mean (SD)	N	Mean (SD)	P-value*
Duration (in days)					
Stay in Makkah before onset of MCD	12	34·1 (53·6)	40	31·5 (46·7)	> 0·05
Period between onset of MCD and admission	58	2·7	90 (3·3)	1·9	< 0·05 (1·7)
Stay in hospital	78	5·4 (5·9)	101	9·2 (6·6)	< 0·0005
Period between onset and diagnosis	58	3·4 (3·7)	90	2·3 (1·9)	< 0·005

* One-tailed t-test between means (SC and CC).

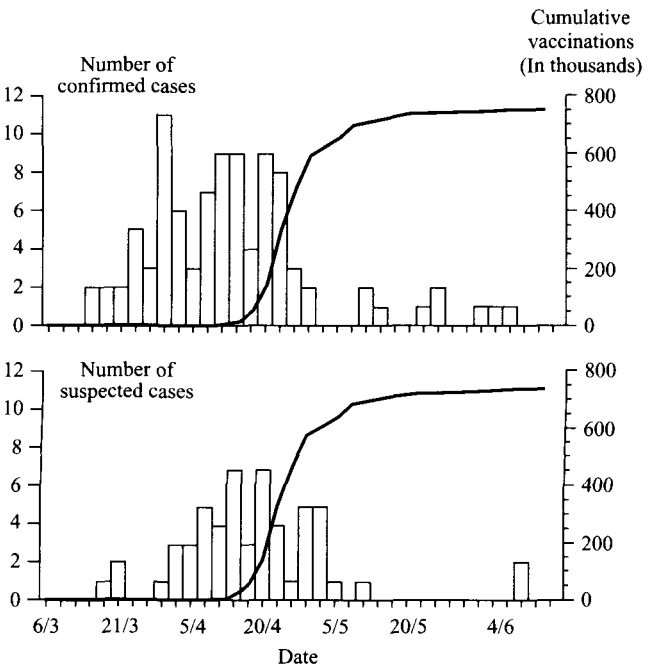

Fig. 1. The upper histogram shows distribution of confirmed cases (CC) of meningococcal disease (MCD) and the lower histogram shows the distribution of suspected cases (SC) of MCD. The line graph shows the cumulative frequency of vaccinations against MCD in temporal relation to the MCD outbreak. Ramadan (5 March through 4 April 1992) is the fasting month for Muslims. Pilgrimage occurs during Dhul Hijja (June 1992). Each point on the X-axis represents a 3-day interval.

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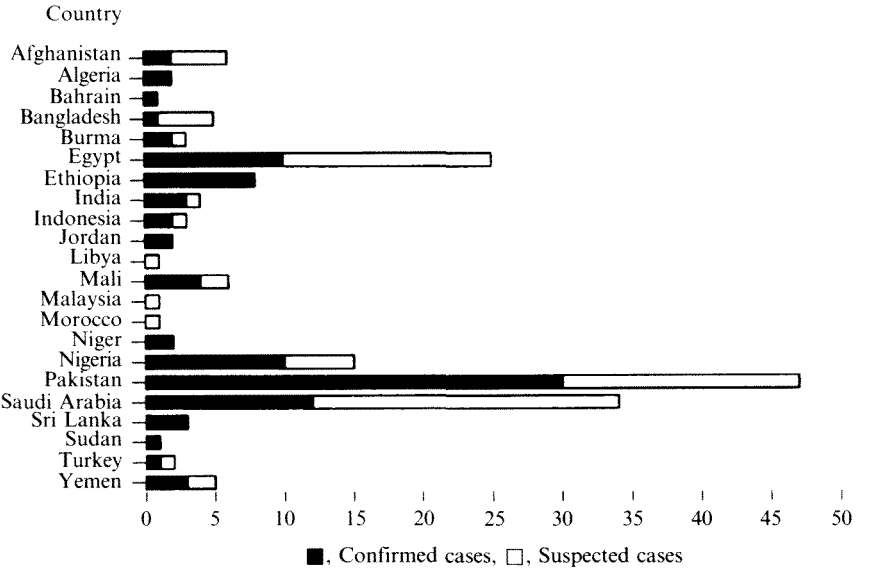

Fig. 2. Nationality of MCD cases, Makkah (March–June, 1992). The nationalities of three confirmed cases and two suspected cases were not known. Denominator populations could not be estimated.

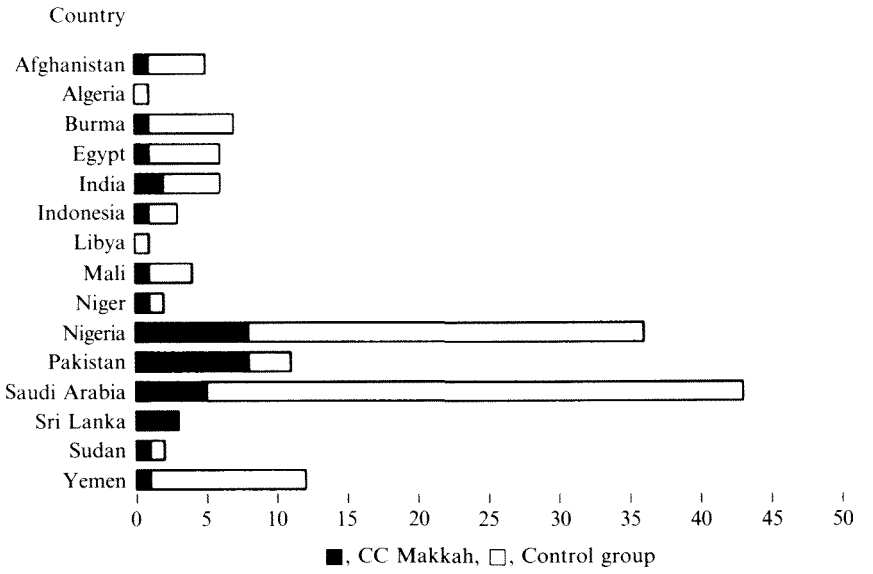

Fig. 3. Nationality of confirmed cases of MCD and control group, Makkah residents only, Makkah (March–June, 1992). The nationalities of three confirmed cases and two suspected cases were not known. Denominator populations could not be estimated.

vaccinated the year before the outbreak were most protected; MCV was of no significant protective value if it had been administered 5 years or more before the outbreak.

When compared with the 112 controls who were also residents of Makkah, CC (Makkah) stated a long list of reasons for not being vaccinated against MCD.

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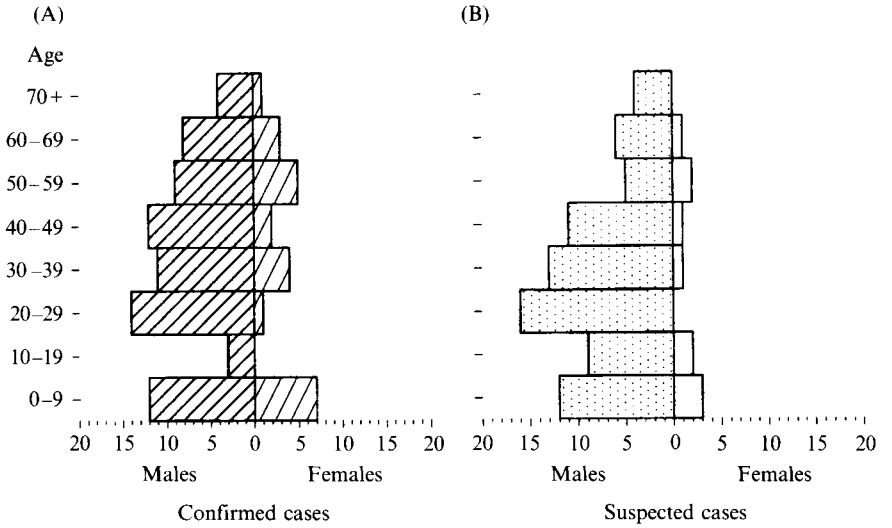

Fig. 4. Age and sex distribution of confirmed (graph A. with hatched lines) and suspected cases (graph B) of MCD. The X-axis shows the number of cases and the Y-axis shows the age groups (10-year interval). Denominator populations could not be estimated.

Table 3 *Vaccination histories and vaccine efficacy, Makkah, 1992*

Vaccination history*	CC	Controls	OR	95% CI	VE%	CI
Never vaccinated (referent group)	15	22	1			
Ever been vaccinated against MCD	9	76	0·17	0·06–0·50	83	50–94
Vaccinated more than 5 years ago	4	19	0·31	0·60–1·22	69	(–22)–94
Vaccinated within the last 5 years	4	25	0·23	0·05–0·90	77	10–95
Vaccinated last year	1	32	0·05	0·00–0·35	95	65–100

* The vaccination histories of 10 Makkah residents were not known.

Seventy-one percent of CC (Makkah residents) and 45% of the controls stated that they did not know about the disease. The other main reasons mentioned were that no vaccination team came to their houses (14·2% of the CC and 9·0% of the controls) and the family head could not take his family to a primary health care centre for vaccination (7·1% of the CC and 14·3% of the controls).

SC showed age and sex distributions comparable with the CC (Table 2. Fig. 4). There was no statistically significant ($P > 0·05$, t-test between two means) differences between CC and SC in educational level, duration of stay in Makkah before the onset of MCD, and the numbers of people sharing the same room. However, the differences between the numbers of people sharing the same house were significant ($P < 0·01$).

DISCUSSION

Why did the outbreak occur during Ramadan for the first time?

Outbreaks of MCD associated with pilgrimage characteristically begin from 2 months to a few weeks immediately preceding the Hajj, when pilgrim populations and crowding progressively increase. This outbreak of MCD was unusual since it began 3 months before the Hajj, during Ramadan, among pilgrims coming for

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Umra. There are several possible explanations for the early occurrence of this outbreak. The strain of meningococcus was the same as the one that caused outbreaks in 1987 and 1988 during Hajj. The ambient temperature during Ramadan in 1992 was less in 1992 (March) than in 1987 and 1988 (May). Vaccination of Hajj visitors from 1989–91 prevented larger Hajj-related outbreaks. The Umra visitors in this outbreak had not been vaccinated. We were not able to document what we suspect is the most likely cause of the outbreak, namely increased and unprecedented crowding during Ramadan.

Why did the outbreak stop?

The precipitous drop in MCD coincident with mass vaccination suggests that the crash program halted the outbreak. However, two other factors should not be ignored. First, the 86% carriage rate measured shortly after completion of vaccination suggests that the pool of susceptible hosts was small. The high carriage rate was observed around the Haram, where the crowd in Makkah is maximal throughout the Hajj period. Broome (1986) reported that carriage rates can reach levels of 40–80% in some closed populations [15]. Second, although new pilgrims were arriving daily to add new uncolonized hosts to the pool of susceptibles, these new pilgrims were protected from overt MCD by MCV given under the well-established Hajj visa requirement. The crash programme probably advanced and accelerated a decline in incident MCD by covering the remaining susceptible Umra visitors and a large number of Makkah residents, particularly those with less exposure to areas of intensive transmission (e.g. around the Haram), persons who had not been vaccinated and undocumented persons.

Was vaccination effective?

The protective effect of previous vaccination was consistent with other studies [16, 17]. Routine vaccination against MCD was effective in preventing MCD in Makkah residents and pilgrims. However, Umra visitors as well as Makkah residents had a poor coverage rate against MCD. A cluster survey, during which 901 Makkah residents were interviewed, showed that only 1·3% (95% CI 0·3–2·1%) of Makkah residents were vaccinated against MCD in 1990–1, 12% (95% CI 9·7–14·3%) in 1991–2 and 72·6% (95% CI 69·5–75·7%) in 1992–3 [18]. The high coverage in 1992–3 was due to the mass vaccination instituted during the outbreak described in this study. No data were available to make a sensible estimate of the proportion of the pilgrims who were vaccinated in each year. Public health education is needed to increase vaccination coverage, especially among Umra visitors. The entire Makkah population needs to be vaccinated every 3–4 years, as vaccine efficacy declines greatly 5 years after administration. The more recent the vaccination history, the more efficacious was the MCV. Poor protection was observed among those who were vaccinated more than 5 years previously.

Moreover, vaccination campaigns need to be supplemented with health education, which should illuminate the seriousness of the disease and the importance of vaccination. The most important reason for not being vaccinated was not knowing about the disease. Makkah city accommodates very diverse ethnic populations. This diversity poses a communication barrier and makes

dissemination of health education messages difficult. Moreover, illegal aliens (undocumented) escape contact with government officials.

Age/sex distribution of cases

More cases were observed among adults. This could be attributed to the nature of the religious rite, which is overwhelmingly performed by adults. Fewer cases were seen among females, an observation that probably relates to the 5:1 male:female ratio among pilgrims, differences in exposure to crowded conditions or use of veils by women (residents of Makkah and some religious visitors). This result should be interpreted with caution because the age- and sex-specific attack ratios could not be calculated due to lack of data on Umra visitors. CCs and SCs shared some similarities. However, the differences between SCs and CCs could be due to inclusion of some cases of other different diseases, which merely happened to share some epidemic temporal pattern, milder forms of MCD since not all SC's underwent full laboratory tests or laboratory investigations were made after initiation of presumptive treatment of MCD. Full history taking was hampered due to language barriers.

High CFR among Pakistanis

An interesting finding in this study was the high case-fatality rate among Pakistani pilgrims, although none of the Egyptian CC died. Moore and colleagues noted that Egypt, unlike many other countries, did not witness a major outbreak in 1987 or 1988 although numerous Egyptian pilgrims attended the 1987 Hajj [1]. This finding suggests the presence of unidentified host or environmental factors that influence the outcome of MCD cases.

Surveillance of MCD

Vaccination remains the key to control, but the role of surveillance is indispensable in control of MCD outbreaks. Although we could not find out the cause of 77 SC, we believe that a sizeable proportion of these SC were due to *N. meningitidis*. The epidemic curve, age, sex and temporal distribution of SC, along with the clinical presentation, were very suggestive of MCD. Thus in places like Makkah, reporting of suspected cases of MCD would increase the sensitivity of the warning system. Cases of MCD were also reported from Jeddah, 72 km northwest of Makkah [19]. Jeddah is the crossroads city for both domestic and international pilgrims. This makes it crucial to establish a good collaborative surveillance system between Makkah and Jeddah in order to abort outbreaks among religious visitors and to prevent spread of communicable diseases between the two cities.

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