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Determinants of case fatality rates of meningococcal disease during outbreaks in Makkah, Saudi Arabia, 1987–97

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SUMMARY

We studied case-fatality rates (CFRs) among cases of meningococcal disease (MCD) admitted to Makkah (Saudi Arabia) hospitals during the period 1988–97. Of 483 cases, 431 (89·2%) were due to strains of serogroup A, 31 (6·4%) to serogroup W135, 16 (3·3%) to serogroup C, and 5 (1·0%) to serogroup B. Eighty-one patients died (case fatality rate (CFR)) 16·8%, 95% CI 13·5%, 20·4%). The CFR in infections due to serogroup A strains was 14·8%, and for other serogroups it was 32·7% (95% CI 20·3%, 47·1%). The CFR of MCD due to *N. meningitidis* serogroup A increased steadily with age ($P<0·05$). Seeking first medical help at a foreign Hajj medical mission and being treated in a non-specialized hospital were associated with a higher case fatality rate.

INTRODUCTION

Meningococcal disease (MCD) is a major health problem in both developing and industrialized countries, especially in sub-Saharan Africa and the Pacific islands, with reported case-fatality rates of 2–13% and with serious sequelae in 3–11% of survivors [1]. Saudi Arabia has been affected frequently by meningococcal disease epidemics. The annual Islamic pilgrimage to the holy city of Makkah, Saudi Arabia, which attracts pilgrims from almost every country, plays a central role in the amplification and dissemination of MCD all over the world [2]. The three main cities in western Saudi Arabia: Makkah, Madinah and Jeddah have each been the site of major outbreaks of MCD in recent years, in 1987 (1841 cases), 1988 (305 cases), and 1992 (102 cases); all were associated with religious visitors. In 1992, the overall CFR was 14·7%, but the CFR for Pakistani patients was 26·8% [2]. The objectives of this study were to determine the CFRs of MCD patients in Makkah hospitals for different strains of *Neisseria meningitidis* and to identify host and socio-demographic factors that influence the CFR among MCD patients in Makkah.

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MATERIALS AND METHODS

Definitions

MCD cases were defined as those patients who presented with an illness with clinical signs of meningitis and/or septicemia in whom *N. meningitidis* was isolated from the cerebrospinal fluid (CSF) or

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blood, or in whose CSF Gram-negative diplococci were visualized, or who had a positive latex agglutination test for *N. meningitidis* in the CSF during the course of an outbreak.

Data sources

All laboratory-confirmed cases of MCD diagnosed in governmental and private hospitals in Makkah are transferred to special wards at King Faisal Hospital, where they receive standardized management. In major outbreaks, such as that in 1992, an additional ward is opened in Al-Zahir Hospital. We reviewed the surveillance system for MCD at the Department of Communicable Diseases, Health Directorate, in Makkah as well the medical records at King Faisal Hospital and the other five governmental hospitals in Makkah (Al-Zahir, Ajyad, Al-Noor, Hera and the Maternity and Children's Hospitals). We reviewed all cases of MCD that occurred during the period from August 1987 and April 1997. We collected socio-demographic, clinical and laboratory variables of the patients, including age, sex, nationality, date of onset of illness, dates of admission and discharge, clinical presentation, underlying illnesses, and results of laboratory investigations.

Statistical analysis

Epi Info (version 6.04b) was used for data management and analyses [3]. Differences between means were calculated using the *t*-test as indicated ($\alpha = 0{\cdot}05$). Exact binomial 95% CI were calculated for variable-specific CFRs. Covariates currently analysed in this study were classified into polychotomous variables. As visits to Makkah are of a religious nature and relate closely to the Islamic lunar calendar and not to the Gregorian calendar, the graph showing the monthly number of cases of MCD utilizes both calendar systems.

RESULTS

Of the 483 cases admitted to the 6 hospitals in Makkah between 1988 and 1997, 421 (87·2%) were culture positive, 58 (12·1%) were confirmed by detection of Gram-negative diplococci in the CSF and latex test, and 4 (0·8%) were confirmed by CSF latex test during an outbreak. Most cases (431, 89·2%) were due to *N. meningitidis* serogroup A; 31 cases (6·4%) were caused by serogroup W135 strains, 16 (3·3%) by serogroup C and 5 (1·0%) by serogroup B strains. During the 5 years from 1988 to 1992, major outbreaks of MCD due to *N. meningitidis* serogroup A occurred in every other year namely 1988, 1990 and 1992. However, from an initial low incidence in 1933, there was tendency for a gradual increase in the annual numbers of cases (Table 1, Fig. 1). The male-female ratio of cases was 2:1, but the CFR was about the same in both sexes (Table 2). Patients ranged in age from less than 1 year to 85 years. The mean ($\pm$S.D.) age of cases of MCD who survived was $33{\cdot}3 \pm 22{\cdot}9$ (median 35 years, IQR 9–50), whereas the mean age of those who died was $48{\cdot}6 \pm 20{\cdot}5$ (median 55 years, IQR: 34–63 ($P < 0{\cdot}05$). Most cases (75%) presented to a hospital within 48 h of the onset of symptoms (range 0–8 days).

In general, outbreaks of MCD started about the ninth lunar month, Ramadan, and ended just before or at the Hajj season in the twelfth lunar month. However, the outbreak of 1988 (1408H) was an exception, as cases of MCD were reported in every month (median of 8 cases per month, range: from 1 case in month 8, *Shaaban*, the lunar month preceding Ramadan, to 48 in month 12, *Dhul Hijja*, the Hajj month (Fig. 1). In the period 1988–97, 336 (77·9%) of the cases that were due to *N. meningitidis* serogroup A were from 7 countries: Pakistan (132 cases, 30·6%), Saudi Arabia (60, 13·9%), Nigeria (42, 9·7%), Yemen (37, 8·5%), India (25, 5·8%), Egypt (24, 5·5%), and Mali (16, 3·7%). Nationality-specific CFRs for MCD due to *N. meningitidis* serogroup A were about 18% in patients from Mali (4/16, 25%, 95% CI 7·3%, 52·4%), Pakistan (30/132, 22·7%, 95% CI 15·9%, 30·8%), Indonesia (2/9, 22·2% 95% CI 2·8%, 60·0%), Turkey (2/11, 18·2%, 95% CI 2·3%, 51·8%), Bangladesh (2/11, 18·2%, 95% CI 2·3%, 51·8%) and Afghanistan (2/11, 18·2%, 95% CI 2·3%, 51·8%).

Of the 483 cases, 81 died (CFR 16·8%; 95% CI 13·5%, 20·4%, Table 1). CFRs were significantly lower for serogroup A disease (14·8%, 64/431, 95% CI 11·6%, 18·6%) than for disease caused by other serogroups (32·7%, 17/52, 95% CI 20·3%, 47·1%, Table 1). Of the 64 deaths due to *N. meningitidis* serogroup A, 13 (20·3%) occurred on the day of admission, 34 (53·1%) within 24–48 h and 45 (70·3%) within 48–72 h admission to hospital (range 0–12 days).

CFR increased steadily with age (Table 2). The

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Table 1. *Case-fatality rate* (*CFR*) *of meningococcal meningitis in Makkah by* N. meningitidis *serogroups*

	Group A			Other groups (B, C and W135)			Total		
Year (Year)*	N†	D‡	CFR	N	D	CFR	N	D	CFR
1988 (1408H)	173	16	9·2	3	0	0	176	16	9·1
1989 (1409H)	36	9	25·0	7	2	28·6	43	11	25·6
1990 (1410H)	32	6	18·8	3	1	33·3	35	7	20·0
1991 (1411H)	7	0	0·0	0	0	0	7	0	0·0
1992 (1412H)	102	15	14·7	0	0	0	102	15	14·7
1993 (1413H)	9	1	11·1	6	2	33·3	15	3	20·0
1994 (1414H)	3	1	33·3	13	5	38·5	16	6	37·5
1995 (1415H)	21	2	9·5	2	1	50·0	23	3	13·0
1996 (1416H)	7	3	42·9	6	1	16·7	13	4	30·8
1997 (1417H)	41	11	26·8	12	5	41·7	53	16	30·2

* H, Year according to Islamic lunar calendar (Hejra).
† N, Number of confirmed cases of meningococcal meningitis.
‡ D, Number of deaths among cases of meningococcal meningitis.

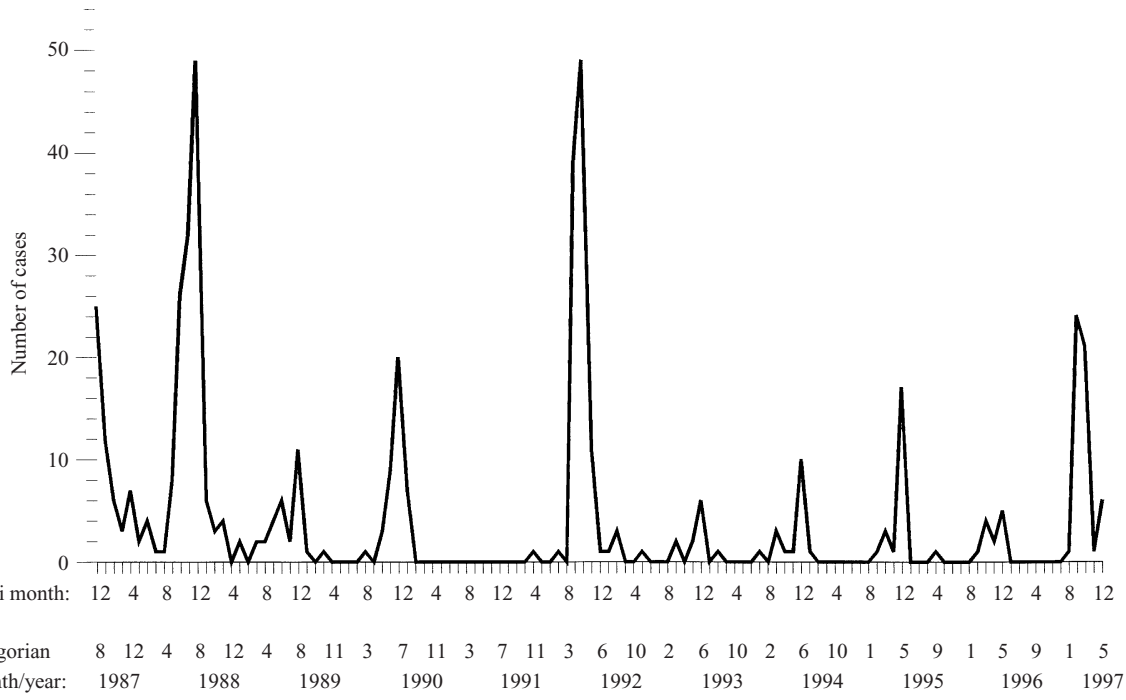

Fig. 1. Monthly number of all notified cases of meningococcal disease, Makkah, Saudi Arabia, 1987–97 (1408–1417 Hijri).

CFR at King Faisal Hospital, where most of the cases were treated, was 15·2% (59/389, 95% CI 11·8%, 19·1%), whereas the overall CFR for the other 5 hospitals was 23·4% (22/94, 95% CI 15·3%, 33·3%). Management of MCD cases outside King Faisal Hospital was associated with a significantly higher CFR (RR 1·5; 95% CI 1·0, 2·4). The highest CFR was noted among religious visitors in Makkah to perform Umra or Hajj, especially those who sought first medical help in foreign Hajj medical missions, of whom 10 out of 28 died (35·7%, 95% CI 18·6%, 55·9%, Table 2).

DISCUSSION

During the period 1988–92, outbreaks of MCD in Makkah occurred every other year during the last 4 months of the Islamic lunar calendar; thereafter, outbreaks occurred yearly. Subsequently, from a low

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Table 2. *Case-fatality of meningococcal meningitis by different regions of the world, residency status, sex, and location of provision of first medical help: results of multivariate analysis*

	Group A				Other groups (B, C and W135)				Total			
	N	D	CFR	95% CI	N	D	CFR	95% CI	N	D	CFR	95% CI
Region of the world												
Europe	2	0	0·0	0–84·2	1	0	0·0	0–97·5	3	0	0·0	0–70·8
North Africa	33	2	6·1	0·7–20·2	3	0	0·0	0–70·6	36	2	5·6	0·7–18·7
Saudi Arabia	60	7	11·7	4·8–22·6	10	1	10·0	0·3–44·5	70	8	11·4	5·1–21·3
Middle East	52	4	7·7	2·1–18·5	2	1	50·0	1·3–98·7	54	5	9·3	3·1–20·3
Southeast Asia	46	6	13·0	4·9–26·3	11	7	63·6	30·8–89·1	57	13	22·8	12·7–35·8
Indian subcontinent	161	35	21·7	15·6–28·9	10	3	30·0	6·7–65·2	171	38	22·2	16·2–29·2
Sub-Saharan Africa	77	10	13·0	6·4–22·6	15	5	33·3	11·8–61·6	92	15	16·3	9·4–24·9
Residency status												
Resident of Saudi Arabia	127	8	6·3	2·8–12·0	9	1	11·1	0·3–48·2	136	9	6·6	3·1–12·2
Hajj religious visitor	113	22	19·5	12·6–28·0	20	10	50·0	27·2–72·8	133	32	24·1	17·1–32·2
Umra religious visitor	123	24	19·5	12·9–27·6	13	5	38·5	13·9–68·4	136	29	21·3	14·8–29·2
Makkah resident	58	7	12·1	5·0–23·3	10	1	10·0	0·3–44·5	68	8	11·8	5·2–21·9
Illegal alien	10	3	30·0	6·7–65·2	0	0	ND	N.C.*	10	3	30·0	6·7–65·2
Sex												
Male	291	42	14·4	10·7–19·1	32	10	31·3	16·1–50·0	323	52	16·1	12·3–20·6
Female	140	22	15·7	10·1–22·8	20	7	35·0	15·4–59·2	160	29	18·1	12·5–25·0
Location of first medical help												
A hospital	337	45	13·4	9·9–17·5	39	13	33·3	19·1–50·2	376	58	15·4	11·9–19·5
A primary health care	64	8	12·5	5·6–23·2	8	3	37·5	8·5–75·5	72	11	15·3	7·9–25·7
Foreign Hajj medical	30	11	36·7	19·9–56·1	5	1	20·0	0·5–71·6	35	12	34·3	19·1–52·2
Age group (in years)												
0–9	96	4	4·2	1·3–10·9	11	1	9·1	0·2–41·3	107	5	4·7	1·5–10·6
10–19	29	2	6·9	0·8–22·8	2	1	50·0	1·3–98·7	31	3	9·7	2·0–25·8
20–29	45	6	13·3	5·1–26·8	5	2	40·0	5·3–85·3	50	8	16·0	7·2–29·1
30–39	61	8	13·1	5·8–24·2	6	1	16·7	0·4–64·1	67	9	13·4	6·3–24·0
40–49	52	9	17·3	8·2–30·3	10	4	40·0	12·2–73·8	62	13	21·0	11·7–33·2
50–59	57	9	15·8	7·5–27·9	5	3	60·0	14·7–94·7	62	12	19·4	10·4–31·4
60–69	53	15	28·3	16·8–42·3	10	3	30·0	6·7–65·2	63	18	28·6	17·9–41·3
>70 years	38	11	28·9	15·4–45·9	3	2	66·7	9·4–99·2	41	13	31·7	18·1–48·1

* N.C., not calculated.

incidence in 1993, there was a gradual increase in the number of cases of MCD. In many other countries, especially in the sub-Saharan meningitis belt (Burkina Faso, Gambia, Ethiopia, and Sudan), epidemics of MCD occurred regularly every 8–12 years following consistent crescendo-decrescendo cyclic patterns [4–6]. The increased frequency of outbreaks of MCD in Makkah may be due to the regular influx of large numbers of visitors. The large reduction in the annual numbers of cases of MCD after 1992 may be attributable to the mass vaccination campaign against MCD in that year, when more than two million persons were vaccinated in Makkah and Jeddah alone. In 1992, all citizens and expatriates resident in Saudi Arabia were encouraged to accept vaccination, thereby reducing the numbers of susceptibles [2, 7]. After the 1988 outbreak of MCD, the Saudi government made vaccination against MCD a mandatory requirement for obtaining an entry visa to the country, especially for Hajj and Umra religious visitors. This regulation was reinforced after the 1992 outbreak [2]. The re-appearance of MCD outbreaks in recent years may be due to a combination of waning immunity in previously vaccinated persons, movement of unvaccinated people into the area during the Islamic sacred lunar months, and some laxity in the implementation of regulations for issuing of visas to Saudi Arabia.

The use of meningococcal vaccine, which confers good immunity against MCD for about 3 years,

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remains the most important action to prevent outbreaks and related deaths. To guard against falsified vaccination certificates, the Saudi government could further reinforce the vaccination requirement for entry visa purposes through close collaboration with authorities or carefully selected centres in countries whose nationals suffer most frequently from MCD. For domestic religious visitors, health education and collaboration with travel agencies and organizers of Hajj missions (*Mutawifs*) would be beneficial. However, early detection of outbreaks by sensitive surveillance is important. Doctors, including those working for foreign missions during Hajj seasons, need to report promptly all suspected cases of MCD. Once an outbreak is confirmed, early and presumptive treatment of suspected cases is justifiable.

The differences in CFR in different hospitals could be due to differences in management protocols. Although the CFR in the Maternity and Children Hospital (MCH) was low (6·7%, 2/30), the number of cases analysed was small with consequent wide 95% CI (0·8–22·1%). However, it is noteworthy that the MCH treated young children and was the only hospital that did not transfer its cases of King Faisal Hospital. The recent increase in the CFR could be due to the relatively small number of cases of MCD diagnosed in Makkah. Generally, the CFR is relatively high when compared with reports from different parts of the world, and when compared with previous reports from other cities in Saudi Arabia. In 1987, the CFR due to MCD in Madinah was 12·1% [8], CFRs, even with optimal antimicrobial treatment, are reported to remain at about 10–15% [6, 9]. In England and Wales, where the CFR has hardly altered in the last 30 years, the overall CFR due to MCD was 12% in 1990 [10], though there may have been some overestimation of CFR due to under-ascertainment of surviving cases. In India, an overall CFR of 16% in children under 15 years has been reported [11], and in Swaziland, an overall CFR as high as 38·8% has been reported. [12]. Sudan reported a CFR of 6·3% [5]. Cases of MCD in Makkah were predominantly adults, with 74% of our patients aged 40 years or older. Adolescents and young adults are less likely to undertake Hajj. Older patients are more likely to be immunocompromised or suffering from some other underlying chronic diseases such as diabetes mellitus. In common with other studies our CFRs increased with age. Most studies from other countries were reporting on cases of MCD in children less than 15 years of age [10, 12–14].

The CFR among patients who sought medical help at a foreign medical mission was nearly three times as high as the CFR in Makkah governmental hospitals. Doctors working for governmental hospitals are usually notified promptly about the appearance of cases of MCD in Makkah, and receive special refresher training in diagnosis and management. Some religious visitors tend to prefer to see doctors of their own nationality working at clinics set up by their own Hajj mission, probably to avoid problems such as language barriers. Foreign Hajj medical missions need to be incorporated into the local health education programmes. Although the nationality-specific incidence of MCD could not be calculated due to unavailability of denominator data, it was clear that patients from the Indian subcontinent and from sub-Saharan Africa had high CFRs. This may be because patients from these two parts of the world tended to be relatively older, staying illegally in Makkah, unaware of the free medical services provided during Ramadan and Hajj seasons, and therefore seeking medical help at governmental medical facilities rather late.

The results of this study need to be interpreted cautiously because they were based on data from hospitals in Makkah, and may not reflect the CFR of MCD diagnosed in other cities in Saudi Arabia. However, in Makkah, all cases of MCD diagnosed at private hospitals were promptly reported and referred to the nearest governmental hospital. Some of the medical charts were not fully completed, and this could have affected estimates of the degree of association of some potential risk factors. Although every year doctors follow a standard protocol for management of cases of MCD, the effect of different treatment regimens was not evaluated in this study.

REFERENCES

1. Scholten RJPM, Bijlmer HA, Valkenburg HA, Dankert J. Patient and strain characteristics in relation to the outcome of meningococcal disease: a multivariate analysis. Epidemiol Infect 1994; **112**: 115–24.
2. AL-Gahtani YM, El Bushra HE, Al-Qarawi SM, Al-Zubaidi AA, Fontaine RE. Epidemiological investigation of an outbreak of meningococcal meningitis in Makkah (Mecca), Saudi Arabia, 1992. Epidemiol Infect 1995; **115**: 399–409.
3. Dean AG, Dean JA, Coulombier D, et al. Epi-Info version 6.04b: a word processing, database, and statistics program for epidemiology on microcomputers Atlanta, Georgia, USA: Centers for Diseases Control and Prevention, 1997.

4. Moore PS. Meningococcal meningitis in sub-Saharan Africa: a model for the epidemic process. Clin Infect Dis 1992; **14**: 515–25.
5 Salih MAM, Hassan HAS, Karrar ZA, *et al*. Features of a large epidemic of serogroup A meningococcal meningitis in Khartoum, Sudan in 1988. Scand J Infect Dis 1990; **22**: 161–70.
6. Riedo FX, Broome CV. Meningococcal disease: a review. Saudi Med J 1991; **12**: 77–83.
7. El Bushra HE, Mawlawi MY, Fontaine RE, Afif H. Meningococcal meningitis group A: successful control of an outbreak by mass vaccination. East Afr Med J 1995; **72**: 715–8.
8. Barlas S, Safdar MUR, Chaudhry SA, Ahamad T, Hashmi IA. Meningococcal disease: clinical profile of 99 patients. Ann Saudi Med 1993; **13**: 237–41.
9. van Deuren M, Dijke BJV, Koopman RJ, et al. Rapid diagnosis of acute meningococcal infections by needle aspiration or biopsy of skin lesions. BMJ 1993; **306**: 1229–32.
10. Strang JR, Pugh EJ. Meningococcal infections: reducing the case fatality rate by giving penicillin before admission to hospital. BMJ 1992; **305**: 141–3.
11. Novelli VM, Lewis RG, Dawood ST. Epidemic group A meningococcal disease in Haj Pilgrims. Lancet 1987; **ii**: 863.
12. Ford H, Wright J. Bacterial meningitis in Swaziland: an 18 month prospective study of its impact. J Epidemiol Commun Hlth 1994; **48**: 276–80.
13. Fakhir S, Ahmed SH, Ahmed P. Prognostic factors influencing mortality in meningococcal meningitis. Ann Trop Paediatr 1992; **12**: 149–54.
14. Lewis LS. Prognostic factors in acute meningococcaemia. Arch Dis Child 1979; **54**: 44–8.