

Group A Meningococcal Carriage in Travelers Returning From Saudi Arabia

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In August 1987, an outbreak of group A meningococcal meningitis occurred during the annual pilgrimage to Mecca, Saudi Arabia, resulting in an attack rate among American pilgrims of 640 per 100 000. To determine risk factors for carriage, throat cultures were taken from passengers arriving on four consecutive flights from Saudi Arabia to the United States. Pilgrims were more likely to be group A meningococcal carriers than were nonpilgrims (relative risk, 11.1; 95% confidence interval, 3.7 to 33.1). Smoking, crowding, and meningococcal vaccination were not significantly associated with group A carriage. Pilgrims complaining of recent fever or sore throat, however, were more likely to be group A carriers, consistent with previous reports linking carriage and disease to preceding viral infections. Serogrouping of invasive meningococcal isolates can be used to monitor for indigenous transmission of this unusual strain in the United States, and we recommend routine vaccination of pilgrims to prevent future outbreaks of meningococcal disease.

(JAMA 1988;260:2686-2689)

EPIDEMIC meningitis is primarily due to group A *Neisseria meningitidis*. Recent epidemics of group A meningococcal meningitis have been reported from Nepal,¹ Finland,² New Zealand,³ and India.⁴ Group A *N meningitidis* is also responsible for ten- to 12-year cycles of epidemic disease in the hyperendemic "meningitis belt" of sub-Saharan Africa.⁵ In contrast, group B *N meningitidis* is the most common meningococcal isolate in the United States. While attack rates can approach 1% during epidemics in developing countries,⁶ the United States is free of epidemic meningitis, with the exception of case clusters and small outbreaks, and has an annual incidence of one to three per 100 000.⁷

Meningococcal carriers are the primary source of *N meningitidis* transmission under both epidemic and endemic conditions. The estimated prevalence of meningococcal carriage in the United States is 5% to 10% under nonepidemic conditions.⁸ In closed pop-

ulations, such as among military recruits, carriage can reach levels of 40% to 80%.⁹ Outbreaks of invasive disease, however, do not necessarily correlate with increased rates of carriage.¹⁰

In this article, we describe a recent outbreak of group A meningitis in travelers returning to the United States from Saudi Arabia. This outbreak provided a unique opportunity to examine meningococcal carriage in persons at high risk for carriage and disease in an epidemic setting.

METHODS

Outbreak Investigation

In August 1987, an outbreak of group A meningococcal meningitis occurred in Moslem pilgrims who had traveled to Mecca and Medina, Saudi Arabia.¹¹ The pilgrimage, or Hajj, occurs annually, and approximately 1.5 million pilgrims worldwide travel to Mecca each year. In 1987, 1250 pilgrims from the United States traveled to Saudi Arabia to participate in the Hajj, which began on Aug 3. Travel to the Hajj requires a special, limited visa and most pilgrims arrived within a month of the beginning of religious rituals.

On Aug 9, New Jersey public health officials reported a case of meningococcal meningitis in a pilgrim returning from Saudi Arabia. Subsequently, several reports were received by the Centers for Disease Control (CDC) indicating that additional returning pilgrims had become ill while in transit or immediately after arrival in the United

States. An advisory was published to alert physicians and public health officials to this problem and to encourage reporting of related cases.

A case was defined as a patient having purulent cerebrospinal fluid with signs and symptoms of meningitis and recent travel to Saudi Arabia. Nine patients fulfilling this case definition were reported to the CDC. Clinical histories were obtained for all patients, and travel histories were obtained from the patients or their next of kin. Bacterial cultures of cerebrospinal fluid were positive for group A meningococcus in four of the nine patients. Three of these isolates were available for serogrouping and analysis for antibiotic resistance by the broth-dilution method.¹²

Meningococcal Carriage in Returning Travelers

To determine the prevalence of group A meningococcal carriage among returning pilgrims and to institute appropriate control measures, four consecutive, nonstop airline flights from Saudi Arabia were met on arrival by public health officials at John F. Kennedy International Airport, New York, on Aug 18, 20, 25, and 27, 1987. Passengers who had visited Mecca or Medina during July or August 1987 were asked to identify themselves. Those who had traveled to either of these two cities were defined as being at high risk even if they had not formally participated in the pilgrimage.

On leaving the airplane, high-risk passengers were given self-administered questionnaires and had samples taken from high in the oropharynx. Questionnaires included information on trip itineraries, contact with known meningitis patients, risk factors for illness, and history of vaccination or chemoprophylaxis against meningococcus. Questions about upper respiratory tract symptoms were added to questionnaires on Aug 20 and, therefore, the analysis of symptoms does not include those of passengers from the Aug 18 flight. Meningococcal chemoprophylaxis was made available to adult passengers at the airport. Since individualized dosing was not possible under these circumstances, parents with infants and children were advised to obtain pedi-

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A preliminary report of this investigation was published in *MMWR* (1987;36:559).

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ric prophylaxis from their family physicians.

A second group of passengers who had not visited either Mecca or Medina were defined as a low-risk group. These low-risk passengers were also interviewed, their throat cultures were taken, and they were given prophylaxis in the same manner as high-risk passengers on a self-selected, voluntary basis. Responses from passengers were studied using univariate cohort analysis.

Microbiology

Throat swabs were plated directly on Mueller-Hinton agar containing 3 mg of vancomycin, 7.5 mg of colistin, and 12.5 mg of nystatin per milliliter (VCN Inhibitor, BBL Microbiologic Systems, Cockeysville, Md). Oxidase tests and identification of serogroups were performed on suspected colonies before the colonies were subcultured onto chocolate agar slants. Sugar-fermentation analysis and broth-dilution antibiograms were performed at the CDC from subcultured colonies. Colonies from two passengers initially serogroup A and oxidase-positive were lost in transport; these passengers were excluded from the analysis.

RESULTS

Meningitis in US Travelers

Nine cases of meningitis in travelers returning from Saudi Arabia were identified, five of which were confirmed as group A meningococcal meningitis (Table 1). Shortly after onset of symptoms in Saudi Arabia, two patients died and the seven remaining patients had onset of symptoms within two days of leaving Saudi Arabia. Eight of the nine patients visited Mecca and Medina during the pilgrimage, and one (patient 7) was a US visitor to Jeddah, Saudi Arabia, who was not on the pilgrimage. The attack rate for Moslem pilgrims from the United States was 640 per 100 000 over a one-month period.

Transmission of meningococcal meningitis between passengers was initially a concern since three passengers (patients 4, 5, and 6) became ill after travel on a single flight. However, in-flight transmission did not appear to be responsible for this disease cluster. Patient 4 was seated far from patients 5 and 6, who were seated together. Patients 5 and 6 traveled together and slept in the same rooms during the pilgrimage. Thus, these two had similar opportunities to acquire the illness from a common source in Saudi Arabia. In addition, patient 4 had onset of symptoms during the flight while patient 5 had symptoms immediately after arrival, a period too short for incubation of

Table 1.—Meningitis in US Travelers Returning From Saudi Arabia, August 1987

Patient No./Sex/Age, y	Onset Date	Onset Location	Cerebrospinal Fluid Results	Hajj*	Outcome
1/M/17	8/9/87	Saudi Arabia	Purulent	Yes	Died
2/M/35	8/9/87	In-flight	Group A by culture	Yes	Alive
3/F/19	8/12/87	Saudi Arabia	Purulent	Yes	Died
4†/F/37	8/13/87	In-flight	Purulent	Yes	Alive
5‡/F/31	8/13/87	New York	Group A + by counter immunoelectrophoresis	Yes	Alive
6†/F/52	8/14/87	New York	Purulent (negative latex agglutination-culture)	Yes	Alive
7/F/69	8/17/87	Atlanta	Group A by culture	No	Alive
8/F/22	8/18/87	Phoenix	Group A by culture	Yes	Alive
9/M/5	8/20/87	Chicago	Group A by culture	Yes	Alive

*See "Methods" section.

†Patients traveling on Aug 13, 1987, flight from Saudi Arabia to John F. Kennedy International Airport, New York.

‡Received antibiotics immediately before hospital admission.

Table 2.—*Neisseria* Carriage in High- and Low-Risk Passengers on Four Flights From Saudi Arabia to New York*

Carrier Status	Risk, No. (%)		
	High	Low	Unknown
<i>Neisseria meningitidis</i> , group A	34 (11)†	2 (1)	0
Throat culture negative	266 (84)†	194 (88)	8 (73)
<i>Neisseria lactamica</i>	8 (3)	20 (9)	2 (18)
Other <i>N meningitidis</i> ‡	10 (3)	5 (2)	1 (9)
Total	318 (101)§	221 (100)	11 (100)

*Passengers arrived at John F. Kennedy International Airport.

†Relative risk in high-risk passengers for group A carriage vs negative throat culture, 11.1 (95% confidence interval, 3.7 to 33.1).

‡Other *N meningitidis* isolates included eight nontypable, two rough, two group Z, two group C, and one each of groups B, X, and W135.

§Does not total 100 because of rounding error.

meningococcal disease.

Meningitis developed in one passenger (patient 8) who returned on the Aug 18 flight from Jeddah, Saudi Arabia. This passenger refused prophylactic therapy because she reported taking rifampin ten days prior to arrival at John F. Kennedy International airport. She developed symptoms of meningitis six hours after entry into the United States. Despite reported use of rifampin, group A meningococcus sensitive to rifampin was isolated from her throat culture.

N meningitidis Carriage

Of 550 passengers on the four flights who were interviewed and whose throats were cultured, 318 were considered to be at high risk, 221 were low-risk volunteers, and 11 had unknown travel histories (Table 2). Thirty-six (7%) of the 550 passengers were group A *N meningitidis* carriers, while 16 (3%) carried other *N meningitidis* strains. Thirty-four (11%) of 318 high-risk persons were group A-positive compared with two (1%) of 221 low-risk passengers, a relative risk of 11.1 (95% confidence interval [CI], 3.7 to 33.1) for travel to Mecca or Medina during the pilgrimage.

Risk Factors for Carriage

To define risk factors for group A carriage, only responses from passengers in the high-risk group were compared. Although the number of high-risk persons declined between the Aug 18 and Aug 27 flights, the proportion of high-risk passengers who were group A carriers did not significantly differ between flights ($P=.807$, χ^2 test for independence). Because of this, high-risk passengers on all flights were considered together in further analysis of risk factors.

Comparison between group A-positive and group A-negative high-risk passengers shows that age, sex, smoking history, and crowding (as measured by number of roommates during the pilgrimage) were not significant risk factors for group A carriage (Table 3). Although meningococcal vaccination has been reported to decrease rates of carriage and to reduce new acquisition of meningococcus,¹³ vaccinated high-risk passengers were as likely to be group A carriers as were nonvaccinated high-risk passengers (9% vs 11%; relative risk, 0.9; 95% CI, 0.3 to 2.7).

Self-reported use of rifampin prophylaxis also did not decrease group A carriage in the high-risk group. Four (14%)

Table 3.—Risk Factors for Group A *Neisseria* Carriage in High-Risk Passengers*

Carrier Status	Age, y (Mean ± SD)	Roommates in Saudi Arabia (Mean ± SD)	Sex, No. (%)		Smokers, No. (%)		Vaccinated, No. (%)		Rifampin Use in Saudi Arabia, No. (%)	
			M	F	Yes	No	Yes	No	Yes	No
<i>Neisseria meningitidis</i> group A	43.9 ± 19.1	2.8 ± 2.2	21 (12)	13 (9)	2 (10)	7 (9)	3 (9)	17 (11)	4 (14)	16 (10)
Group A—negative*	42.0 ± 17.6	2.5 ± 4.0	152 (88)	130 (91)	19 (90)	71 (91)	30 (91)	142 (90)	24 (86)	142 (90)
Total†			173 (100)	143 (100)	21 (100)	78 (100)	33 (100)	159 (101)‡	28 (100)	158 (100)
Relative risk (95% confidence interval)			1.3 (0.7-2.5)		1.1 (0.2-4.8)		0.9 (0.3-2.7)		1.4 (0.5-4.0)	

*Combined passengers with negative throat cultures, *Neisseria lactamica*, and other, non-group A *N meningitidis* strains.

†Totals vary since some questionnaires were only partially completed.

‡Does not total 100 because of rounding error.

Table 4.—Symptoms in High-Risk Passengers

	Fever, No. (%)		Sore Throat, No. (%)		Cough, No. (%)	
	Yes	No	Yes	No	Yes	No
<i>Neisseria meningitidis</i> group A	6 (30)	14 (9)	12 (19)	8 (7)	11 (14)	9 (9)
Group A—negative*	14 (70)	139 (91)	51 (81)	111 (93)	67 (86)	92 (91)
Total	20 (100)	153 (100)	63 (100)	119 (100)	78 (100)	101 (100)
Relative risk (95% confidence interval)	3.3 (1.4-7.7)		2.8 (1.3-6.4)		1.6 (0.7-3.6)	

*Combined passengers with negative throat cultures, *Neisseria lactamica*, and non-group A *N meningitidis* strains.

of 28 high-risk passengers who reported rifampin use were group A carriers compared with 16 (10%) of 158 (relative risk, 1.4; 95% CI, 0.5 to 4.0) passengers who did not report taking rifampin. Passengers taking rifampin had a lower rate of non-group A meningococcal carriage than passengers without prophylaxis, although this difference was not statistically significant (data not shown). Rifampin resistance, however, did not contribute to failure of prophylaxis since all meningococcal strains tested from both patients and carriers were sensitive to rifampin. Additionally, all strains were resistant to sulfadiazine and sensitive to ceftriaxone, penicillin G, and chloramphenicol.

Despite the lengthy flight (13 hours), on-board transmission did not appear to be a major source of group A meningococcal acquisition. Seat assignment diagrams of the four flights (not shown) failed to reveal clustering of carriage among passengers. Lack of in-flight transmission is also supported by the low rate of carriage among the 221 low-risk passengers. Although one of the two low-risk carriers was an employee of the airlines and may have acquired his infection from passenger contact, both low-risk carriers lived in Jeddah, Saudi Arabia, a city with a large number of reported meningitis cases.

Symptoms in High-Risk Carriers

Group A carriage was significantly associated with upper respiratory tract infection (URI) symptoms (Table 4). When carriage was stratified by risk group, 30% of high-risk passengers

complaining of fever during their trip were group A carriers, compared with 9% of afebrile high-risk passengers (relative risk, 3.3; 95% CI, 1.4 to 7.7). Similarly, 19% of high-risk passengers complaining of sore throat were group A carriers, compared with 7% of asymptomatic passengers (relative risk, 2.8; 95% CI, 1.3 to 6.4). Cough, however, was not significantly associated with group A carriage. Carriage of *Neisseria lactamica* or other *N meningitidis* serogroups was not associated with any URI symptoms in high-risk passengers.

COMMENT

This outbreak was unusual because of its high attack rate and unique potential for dissemination of an epidemic strain throughout the world. The attack rate in American pilgrims was approximately 3500 times higher than the incidence of meningococcal disease for a comparable period in the general US population. Given the high attack rate among American Hajjis and the explosive nature of this outbreak, we recommend that vaccination be considered for all pilgrims in the future.¹⁴ A quadrivalent meningococcal vaccine effective against *N meningitidis* serogroups A, C, W135, and Y is currently licensed for use in the United States.

The epidemiology of meningococcal carriage and invasive disease is complex and poorly understood. However, since the Hajj is an annual event, it is appropriate to seek explanations for the occurrence of epidemic meningitis during the 1987 pilgrimage. Although acquisition of carriage is clearly a risk factor for

invasive illness, other cofactors probably play an important role in the subsequent development of disease. It is possible that an unusually virulent group A strain was involved in this outbreak or that circulating viral illnesses increased the susceptibility of pilgrims to meningococcal infection.

In our study, high-risk passengers complaining of URI symptoms were two to three times more likely to be carriers than were asymptomatic passengers. We were not able to determine whether these symptoms were the result of meningococcal acquisition itself⁶ or a preceding viral illness that facilitated acquisition. Symptoms of URI have previously been shown to be closely associated with carriage in household contacts of sporadic cases,¹⁶ and Young et al¹⁷ reported an outbreak of meningococcal meningitis in institutionalized patients who had recently had influenza A. Other investigators^{18,19} have also suggested a role for viral respiratory infections in predisposing patients to invasive disease. Additional studies are needed to clearly define the role of antecedent viral infections in both meningococcal carriage and disease.

There was no evidence of in-flight transmission of carriage among passengers on these four flights. Close, prolonged, person-to-person exposure, such as among household or day-care contacts, is generally required for transmission of meningococcal meningitis.^{20,21} For example, classroom contacts of students with meningitis are not, in general, at increased risk for disease,²² although isolated cases of transmission

have been documented in high school contacts²³ and in students riding on the same school bus (unpublished observation [L.H.H.]). It is probable that the limited contact between passengers in our study was insufficient for significant in-flight transmission of carriage. We cannot, however, rule out the possibility that culturing passengers' throat swabs after the flight was insensitive for detecting in-flight transmission.

There are conflicting reports^{9,24} on the effects of meningococcal vaccination on carriage of meningococcus. In our study, rates of carriage did not significantly differ between vaccinated and unvaccinated pilgrims. Additionally, carriage rates were not lowered by rifampin use, although rifampin has been repeatedly shown to be effective chemoprophylaxis.⁹ These results should be interpreted with caution since it was not possible to validate rifampin use or vaccination history during our study. Since rifampin resistance did not occur in any of the group A meningococcal isolates, these findings may reflect either unreliable recall by passengers or reinfection with group A meningococcus after taking rifampin. Low non-group A meningococcal carriage rates in passengers taking rifampin suggest that reinfection with group A meningococcus may have been the important factor in failure of prophylaxis.

Oral rifampin (adults: 600 mg every 12 hours for four doses; children over 1

month old: 10 mg/kg every 12 hours for four doses) is the drug of choice for prophylaxis of contacts of meningitis patients. Several new antibiotics (ciprofloxacin hydrochloride,²⁵ ceftriaxone²⁶) show promise as alternative chemoprophylactic agents. While chloramphenicol and penicillin G are often used for treatment of meningococcal meningitis, they do not achieve high drug levels in saliva, and should not be used for chemoprophylaxis. Patients recovering from meningococcal disease should receive a course of rifampin chemoprophylaxis to eliminate residual meningococcal carriage.²⁷

This outbreak has allowed the widespread dissemination of a group A meningococcal strain with major epidemic potential. Widespread epidemics of meningococcal disease have not occurred in the United States since the late 1940s, and it is unlikely that this importation of group A meningococcal cases will significantly increase endemic disease. Nevertheless, we were only able to administer prophylaxis to one quarter of the total population of US travelers to the 1987 Hajj. It is reasonable to assume that a substantial reservoir of group A carriers arrived in the United States without adequate prophylaxis. Since meningococcal meningitis shows a seasonal increase during the winter in the United States,²⁸ it is possible that secondary cases may be seen during winter months.

Group A meningococcus is an uncommon meningococcal serogroup in the United States. In a 1986-1987 population-based study of meningitis in five states and one major metropolitan center, none of the 700 meningococcal isolates reported were group A (unpublished data, CDC Meningitis Active Surveillance Project, 1986-1987). Of meningococcal cases reported to the CDC between 1978 and 1981, only 4.7% of isolates were group A.²⁸ Therefore, serogrouping of meningococcal isolates will be an important means of monitoring indigenous transmission of this imported strain. This outbreak reaffirms the importance of serogrouping meningococcal meningitis isolates and reporting of meningitis cases to public health authorities.

Passive CDC surveillance data from the United States have not detected increased indigenous transmission of group A *N meningitidis* as of August 1988. However, secondary cases from this epidemic strain have been reported in other host countries.

The authors would like to acknowledge the advice and assistance of H. Ragazzoni, DVM, New Jersey State Department of Health; Stephen Schultz, MD, and S. Shahidi, MD, New York City Department of Health; the US Public Health Service Quarantine Office, John F. Kennedy International Airport, New York; and the medical staff of the John F. Kennedy International Airport Health Clinic, New York. The authors would also like to thank Allen Hightower, MS, for advice on statistical techniques; Clyde Thornsberry, MD, PhD, and Sheila Stocker, MS, for antibiogram analysis of the cultures; and Ben Schwartz, MD, for help in preparing this manuscript.

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