

Incidence of Hajj-associated febrile cough episodes among French pilgrims: a prospective cohort study on the influence of statin use and risk factors

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Abstract

A prospective epidemiological study was conducted to evaluate the incidence of febrile cough episodes among adult Muslims travelling from Marseille to Saudi Arabia during the Hajj pilgrimage and to assess if use of statin had an influence on this incidence. In total, 580 individuals were presented with a questionnaire. A significant proportion of individuals had chronic medical disorders, e.g. diabetes mellitus (132, 22.8%) and hypertension (147, 25.3%). Pilgrims had a low level of education and a low employment rate. Sixty (10.3%) were treated with statins for hypercholesterolemia. Four hundred and forty-seven pilgrims were presented a questionnaire on returning home. A total of 74 travellers (16.6%) experienced fever during their stay in Saudi Arabia (67 attended a doctor) and 271 (60.6%) had cough (259 attended a doctor); 70 travellers with cough were febrile (25.9%). Seventy per cent of the travellers who suffered cough episodes developed their first symptoms within 3 days, suggesting a human to human transmission of the responsible pathogen, with short incubation time as evidenced by a bimodal distribution of cough in two peaks at a 24 h interval. None of demographical and socioeconomic characteristics, underlying diseases or vaccination against influenza significantly affected the occurrence of cough. Diabetes correlated with an increased risk of febrile cough (OR = 2.02 (1.05–3.89)) as well as unemployment (OR = 2.22 (0.91–5.53)). Use of statins had no significant influence on the occurrence of cough and/or fever during the pilgrimage. This result suggests that while treatment with a statin has been demonstrated to reduce the mortality from severe sepsis associated with respiratory tract infections, it probably does not play a role in the outcome of regular febrile cough episodes as observed in the cohort studied here.

Keywords: Acute respiratory infection, Hajj, La Mecca, pilgrim, Statin

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Introduction

Each year, approximately 2000 Muslims travel from Marseille to participate in the Hajj, gathering with over two million pilgrims from all over the world. Health risks during the Hajj are a critical issue due to the extreme congestion of people [1]. Infectious diseases represent a major problem during the pilgrimage with acute respiratory infections (ARI) as the most common cause of admission to hospital [2–4]. Hajj pilgrims during their 1-month stay in Saudi Arabia experience relatively homogeneous accommodation conditions, and

undertake identical rituals, while retracing the footsteps of the Prophet Mohammed, thus being very likely exposed to the same risk of ARI. In recent years, several non-randomized studies have linked statin use with decreased risk of severe sepsis or death from severe infections, including pneumonia [5–7]. Recent prospective cohort studies confirmed previous observations [8–12] while another suggested that the apparent beneficial effect of statins probably reflected a ‘healthy user’ effect, as statin users appeared to be younger, healthier, better educated, and socially and economically more privileged compared to non-statin users [13]. These controversial findings also raised questions about the potential role of statins in the prophylaxis of infectious diseases such as pandemic influenza [14]. Muslims departing from Marseille to participate in the Hajj have been found to have a median age of 61 years, with more than one third being over 64 years old [15], and are therefore likely to use

statins in a significant proportion. We conducted a prospective epidemiological study to evaluate the incidence of febrile cough episodes among Hajj pilgrims from Marseille and to assess if statin use could have an influence on this incidence. The socio-economic situation and health characteristics of the travellers were not consistent with the hypothesis of a 'healthy user' effect.

Materials and Methods

Study population

A prospective cohort study was carried out in the Marseille Travel Medicine Centre (Hôpital Nord) from 4 November to 8 December 2006. Participants in the survey were pilgrims in preparation for the Hajj pilgrimage enrolled in the meningococcal vaccination campaign to satisfy compulsory vaccination requirements. Pilgrims older than 18 years were included on a voluntary basis and participants were asked to give written consent. Pre-travel questionnaires were presented orally, before vaccination, in French, in Arabic or in French and Arabic, depending on the language fluency level of the participants. Post-travel questionnaires were presented by telephone.

Questionnaires

The pre-travel questionnaire included demographic factors (age, gender, location of residence), indicators of immigration status (country of birth and duration of stay in France), socio-economic indicators (level of education, employment, type of housing, rooms per person and household, complementary health insurance modalities), health status indicators (diabetes, hypertension, chronic respiratory diseases, statin use, vaccination coverage against influenza) and number of previous travels to Saudi Arabia.

The post-travel questionnaire included travel indicators (duration of stay, food and housing conditions) and data about travel-associated diseases (medical consultation, hospitalization, occurrence of cough with or without fever, time of manifestation and duration of symptoms). Cough was defined as occurrence of cough with or without sputum in an individual without chronic cough and subjective aggravation of cough in individuals suffering from chronic respiratory diseases. Fever was defined as subjective feeling of fever. Pilgrims were considered as lost in follow up after three failed attempts to reach them by phone.

Analysis

Data were recorded anonymously in a Microsoft Access database and transferred to EPINFO 6.0 software (CDC,

Atlanta, GA, USA) for univariate statistic analysis. Differences in proportions were evaluated using the chi-square test. As selection procedure, a two-tailed p value ≤ 0.25 was considered as significant [16]. Multivariate analysis was performed using the SPSS version 15 software program (SPSS, Inc., Chicago, IL, USA). Factors with a p value < 0.25 in univariate models were included in a multivariate model, as suggested in the classical work of Mickey and Greenland [16]. Sex, age and statin use were also included in the model. A stepwise procedure based on likelihood ratio criteria was used in order to obtain the best criteria with the lowest Akaike criteria (AIC) [17–19]. For the final model, a two-tailed p value ≤ 0.05 was considered as significant.

Results

Among 650 vaccinees preparing for the Hajj pilgrimage, 580 voluntarily participated in the study, yielding a response rate of 89.2%.

Respondents had an average age of 58 years (range 20–85 years) with a sex ratio (M/F) of 1.32 (Table 1). A total of 217 travellers were living in Marseille (37.4%), 357 in other parts of southern France (61.6%); information was not available in six cases (1.0%). Most of the pilgrims were born outside of France, with 88.8% having been born in North Africa. The mean duration of stay in France was 32 years (range 0–72 years). A proportion of 83.1% of travellers had a primary school education or below. Thirty-four per cent of individuals were retired.

Among those under 65 years which is the age of retirement in France, only 10.9% were employed. A proportion of 47.1% was living in state-subsidized housing and 49% received state subsidies for payment of rent. Only 19.8% were property owners. Among 41.2% of individuals, the household allocation was less than one room per person. A proportion of 26.6% of travellers was covered by the state-financed complementary health insurance which is accessible to insolvent individuals and 45.2% had a self-financed private complementary health insurance.

A proportion of 7.4% were covered under the state-financed full health insurance coverage in cases of chronic and debilitating disease. Forty-three per cent of the pilgrims declared to suffer from chronic diseases, including 22.8% suffering from diabetes, 25.3% from hypertension and 4.0% from chronic respiratory disease. A proportion of 10.3% was treated with statin for hypercholesterolaemia. A proportion of 34.3% of travellers reported to have been vaccinated against influenza in 2006. A total of 414 individuals (71.4%) had never travelled to Saudi Arabia, 89 (15.3%) had made a

TABLE 1. Demographics, immigration status and socio-economic indicators in 580 Hajj pilgrims departing from Marseille

Variables	Number (%)
Age class	
20–44 years	80 (13.8)
45–64 years	295 (50.9)
≥65 years	205 (35.3)
Gender	
Male	330 (56.9)
Female	250 (43.1)
Location of residence	
Marseille	217 (37.4)
South France (out of Marseille)	357 (61.6)
Unknown	6 (1.1)
Country of birth	
Algeria	269 (46.4)
Morocco	149 (25.7)
Tunisia	97 (16.7)
France	37 (6.4)
Comoros	11 (1.9)
Other	17 (2.9)
Duration of stay in France ^a	
0–10 years	56 (10.4)
11–30 years	157 (20.0)
≥31 years	328 (60.6)
Education level	
<CS	398 (68.6)
CS	84 (14.5)
Bac	20 (3.4)
>Bac	56 (9.7)
Employment	
Retired	200 (34.5)
Employed	63 (10.9)
Non employed	263 (45.3)
Unknown	54 (9.3)
Type of housing	
Shelter	29 (5)
Social housing	273 (47.1)
Renter of property	125 (21.6)
Owner of property	115 (19.8)
Other	38 (6.5)
Household rooms per person	
<1	239 (41.2)
≥1	299 (51.6)
National subsidies for payment of rent	
Yes	284 (49.0)
No	240 (41.4)
Complementary health care insurance modalities (CHI)	
State-financed CHI	154 (26.6)
Self-financed private CHI	262 (45.2)
No CHI	121 (20.9)
FHIC	43 (7.4)

CS, certificate of study (primary school); Bac, baccalaureate; FHIC, state-financed full health insurance coverage due to suffering a chronic and debilitating disease.

^aImmigrants only.

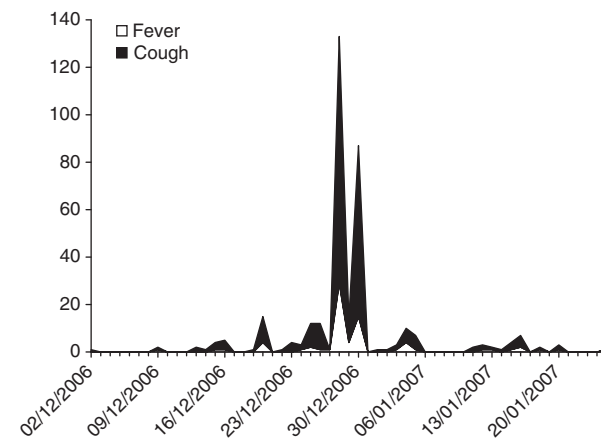
previous pilgrimage to Mecca and 77 (13.3%) had travelled several times to Saudi Arabia before.

A total of 447 pilgrims (77.1%) were presented a questionnaire upon returning home, six individuals renounced travel (1.0%) and the remaining (21.9%) were lost to follow-up. The mean time between return and presentation of the questionnaire was 27 days (range 1–98 days). No significant variation was observed between the 447 travellers who answered the questionnaire and the 580 enrolled pilgrims regarding demographic, immigration and socio-economic characteristics, as well as underlying chronic diseases.

TABLE 2. Travel-related diseases in 447 Hajj pilgrims returning from Saudi Arabia

Variables	Number (%)
Medical consultation	
After travel	29 (6.5)
During travel	241 (53.9)
Symptoms during travel	
Fever	74 (16.6)
Cough	271 (60.6)
Cough and fever	62 (13.9)
Reason for attending a doctor during travel (n = 270)	
Fever	70 (25.9)
Cough	259 (95.9)
Rhinitis	9 (3.3)
Skin infection	1 (0.4)
Urinary tract infection	1 (0.4)
Other	6 (2.2)

The mean duration of the pilgrimage was 30 days (range 14–63 days). The vast majority of pilgrims declared to have been housed and to have eaten together (99.8% and 96.4%, respectively). As shown in Table 2, a proportion of 53.9% of travellers attended a doctor during travel and 6.5% did so after travel. Nine individuals were hospitalized (two in Saudi Arabia, one in Algeria and six upon returning to France). Among the six patients hospitalized in France, two had a respiratory tract infection. *Haemophilus influenzae* was identified as the responsible pathogen in one of these two patients who was also suffering from diabetes. Among the four other hospitalized patients, two had unstable diabetes mellitus and two had haematological disorders. A total of 74 travellers (16.6%) experienced fever during their stay in Saudi Arabia (67 attended a doctor) and 271 (60.6%) had cough (259 attended a doctor). Just over 25% of the travellers with cough were febrile. Dates of beginning of fever and cough are shown in Fig. 1. A first peak was observed on 28 December, followed by a second peak on 30 December. The mean duration of fever was 3 days (range 1–15 days) while the mean duration of cough was 11 days (range 2–30 days).

**FIG. 1.** Occurrence of cough and fever in Hajj pilgrims (number of cases as expressed by date of first symptoms).

None of demographical and socio-economic characteristics of pilgrims significantly affected the occurrence of cough. Similarly, previous travel to Saudi Arabia, diabetes, hypertension and chronic respiratory diseases, as well as vaccination against influenza had no significant influence on the occurrence of cough during the pilgrimage (Table 3). When considering only the cases of cough associated with fever, travellers with diabetes appeared to have an increased risk compared to other patients in univariate analysis (OR = 2.02 (1.1–3.7), *p* 0.02). Similarly, individuals of <65 years and unemployed had a greater risk of cough associated with fever (OR = 2.22 (0.98–5.03), *p* 0.05). Several factors appeared to be related to febrile cough, without reaching statistical significance. None of the other factors influenced the risk of febrile cough (Table 3). When adjusting factors for multivariate analyses, only diabetes remained associated with a higher risk of febrile cough (OR = 2.85 (1.37–5.92), *p* 0.005).

Statin users were significantly older compared to other travellers (mean age = 62.7 years, range 28–85 years vs. 55.7 years, range 23–78; *p* 0.004). However, sex ratio (1.00

vs. 0.75), education level \leq certificate of primary school study (93.2% vs. 85.6%), employment rate among individuals under 65 years (9.7% vs. 20.3%), household rooms per person <1 (49.1% vs. 43.9%), national subsidies for rent payment (58.9% vs. 53.6%) and state-financed complementary health care insurance (30.0% vs. 26.2%) were not statistically different in statin users and non-users. Use of statin had no significant influence on the occurrence of cough and or fever during the pilgrimage.

Discussion

In the present study, we observed that Hajj pilgrims from Marseille represent a specific population of travellers with more than one third being geriatric patients, mainly originating from North Africa. This is consistent with previous findings [15]. Of particular concern was the finding that a significant proportion of individuals had chronic medical disorders, e.g. diabetes mellitus and hypertension. Similarly, high rates of diabetes and hypertension were found in patients

TABLE 3. Risk factors among travellers with cough and fever

Variables	Travellers without cough and fever (n = 176)	Travellers with cough, non-febrile (n = 201)	Univariate analysis (travellers with cough non-febrile versus travellers without cough and fever)		Travellers with cough and fever (n = 70)	Univariate analysis (travellers with cough and fever versus travellers without cough and fever)	
			OR (IC 95%)	P		OR (IC 95%)	P
Age – mean (SD) [†]	57.1 (12.8)	57.9 (11.7)	–	0.51	57.7 (12.3)	1.00 (0.98–1.02)	0.74
Sex – number (incidence rate %)							
Male	94	110 (53.9)	0.95 (0.62–1.46)	0.79	38 (28.8)	0.97 (0.69–1.53)	0.90
Female	82	91 (52.6)			32 (28.1)		
Education level \leq CS [†]							
Yes	127	131 (50.8)	0.72 (0.45–1.15)	0.14	46 (26.6)	0.74 (0.39–1.41)	0.32
No	49	70 (58.8)			24 (32.9)		
No Employment ^{a,†}							
Yes	78	96 (55.2)	1.17 (0.66–2.08)	0.56	41 (34.5)	2.22 (0.98–5.03)	0.05
No	38	40 (51.3)			9 (19.1)		
Household rooms per person <1 [*]							
Yes	72	87 (54.7)	1.01 (0.64–1.57)	0.98	29 (28.7)	0.97 (0.54–1.73)	0.91
No	89	107 (54.6)			37 (29.4)		
Previous travel to Saudi Arabia [*]							
No	122	148 (54.8)	1.26 (0.78–2.03)	0.31	50 (29.1)	1.17 (0.63–2.16)	0.63
Yes	54	52 (49.1)			19 (26.0)		
Diabetes [†]							
Yes	38	44 (53.7)	1.02 (0.60–1.72)	0.94	25 (39.7)	2.02 (1.1–3.7)	0.02
No	138	157 (53.2)			45 (24.6)		
Chronic respiratory disease							
Yes	9	6 (40.0)	0.94 (0.57–1.55)	0.79	4 (21.1)	1.13 (0.34–3.78)	0.85
No	167	195 (53.9)			66 (15.4)		
Hypertension							
Yes	43	51 (54.3)	1.05 (0.64–1.73)	0.83	20 (31.7)	1.24 (0.66–2.3)	0.50
No	133	150 (53.0)			50 (27.3)		
Statin use [‡]							
No	157	181 (53.6)	1.10 (0.53–2.25)	0.79	61 (28.0)	0.82 (0.35–1.91)	0.65
Yes	19	20 (51.3)			9 (32.1)		
Vaccination against influenza							
No	119	122 (50.6)	0.67 (0.42–1.07)	0.07	45 (27.4)	0.79 (0.43–1.43)	0.43
Yes	50	76 (60.3)			24 (32.4)		

CS, certificate of study (primary school).

^aEmployment rate in individual under 65 years only (%).

^{*}Missing data.

[†]Variables entered in the multivariate model.

requiring admission to tertiary-care hospitals during the Muslim pilgrimage [20]. We also observed that the level of education of Hajj pilgrims was particularly low, with a proportion of 83.1% of individuals with a level of education below that of a certificate of primary school education compared to 42.3% in the total immigrant population and 24.1% in the general population of south eastern France (PACA) [21]. The pilgrim employment rate was seven-times lower and the proportion of pilgrims living in social housing in state-owned property was twice that of the total immigrant population in the same region [21].

These results, together with an overall low rate of vaccination against tetanus, diphtheria, poliomyelitis and influenza [15], suggest that Hajj travellers departing from Marseille represent a category of travellers particularly at risk for travel-related diseases and that their socio-economic conditions should be considered during the pre-travel visit regarding cost-effective vaccines.

In our survey, we observed a very high attack rate of cough episodes (60%), higher than that described in other studies. One study reported an incidence of ARI of 40% within a group of pilgrims from Riyadh [22]. A study based on clinical criteria of influenza-like illness among pilgrims from Pakistan reported rates of 36% in influenza-vaccinated pilgrims and 62% in pilgrims not vaccinated against influenza [23]. Another study involving English pilgrims, based on seroconversion rates, showed an attack rate of 30% among the vaccinated and 41% among the non-vaccinated participants [24]. Finally, an ARI attack rate of 26% was recently observed among medical team members treating pilgrims in Saudi Hospitals [25]. Vaccination coverage against influenza did not influence the occurrence of ARI in our experience, which strongly suggests that influenza virus was not the pathogen responsible for the observed symptoms. When investigating the pathogens causing respiratory tract infections in hospitalized patients during the Hajj, *H. influenzae*, *Klebsiella pneumoniae* and *Streptococcus pneumoniae* appeared to be the most common pathogens (30%) in one study [26], while *Mycobacterium tuberculosis* was the most common pathogen (20%) identified in a study on community-acquired pneumonias during the 1994 Hajj [27]. Viral pathogens are also commonly identified during the Hajj, representing 11–20% of pathogens responsible for upper respiratory tract infections in hospitalized pilgrims with Influenza A and B virus, rhinovirus and adenovirus being the most common [26–29].

Seventy per cent of the travellers who developed cough episodes in our study developed their first symptoms within 3 days, suggesting human to human transmission of the responsible pathogen, with short incubation time as evi-

denced by the bimodal distribution of cough in two peaks at a 24 h-interval.

Statin use in this study was not associated with a reduction in the occurrence of travel-associated infections during the Hajj pilgrimage. Occurrence of cough episodes, duration of cough and association with fever were similar in travellers treated with statins and control travellers. To our knowledge, this is the first prospective study investigating a potential role of statins in the outcome of cough episodes in a cohort of individuals exposed to the risk. This result suggests that, while treatment with statin has been demonstrated to reduce the mortality of severe sepsis associated with respiratory tract infections [5–7], it does not play a medically significant role in the outcome of regular cough episodes as observed in the cohort studied here. However, the study involved limited numbers of statin users so that no definitive conclusions should be made.

In this study, we observed that statin users were older compared to non-users, but the level of education and socio-economic characteristics were similar in both groups. None of the demographic and socio-economic characteristics of travellers affected the incidence of febrile cough in our experience. However, the study does not have the sufficient size for the examination of several risk factors, e.g. a chronic respiratory condition. Diabetes mellitus appeared to be correlated with febrile cough in the cohort studied here. It remains uncertain whether diabetes is an independent risk factor for increased incidence or severity of common upper or lower respiratory tract infections [30]; however infections caused by certain micro-organisms (*Staphylococcus aureus*, Gram-negative organisms and *M. tuberculosis*) occur with increased frequency. Infections due to other micro-organisms (*S. pneumoniae* and influenza virus) are associated with increased mortality and morbidity [31].

Our study highlights the fact that respiratory tract infections are very likely to occur during the Hajj pilgrimage independently of vaccination coverage against influenza. Overcrowding and continuous close contact, notably in the desert plains of Mina and Arafat where accommodation in collective tents is necessary, greatly increases the spread of respiratory tract infections. Under these conditions a single case of severe acute respiratory syndrome during the Hajj may cause an epidemic of unprecedented scale. During pre-Hajj consultation such an event should be considered in counselling travellers. Hand disinfection with alcohol-based scrubs should be recommended as it was proven to protect from ARI development; it should be acceptable to most pilgrims given the religious insistence on ritual purity before the five daily prayers [32]. The Saudi Arabian Ministry of Health has recommended that masks be used to minimise

droplet spread [33]. However, regular use of surgical face-masks was recently shown to offer no significant protection against ARI, and intermittent use of surgical-type masks is associated with increased risk of infection [25]. Furthermore, many Muslims consider covering of the face during the Hajj to be prohibited; therefore general compliance with this advice is unlikely. Vaccination against *H. influenzae* and *Pneumococcus* should be recommended to travellers suffering from chronic respiratory disease and diabetes mellitus conditions. Vaccination against diphtheria, tetanus, poliomyelitis and pertussis should be updated when required and vaccination against influenza systematically proposed.

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Transparency Declaration

The authors state that they have no conflicts of interest.

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