

Infections in travellers returning to Turkey from the Arabian peninsula: a retrospective cross-sectional multicenter study

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Received: 4 February 2016 / Accepted: 17 February 2016 / Published online: 10 March 2016
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Abstract Mass gatherings pooling people from different parts of the world—the largest of which is to Mecca, Saudi Arabia, for Hajj—may impose risks for acquisition and dissemination of infectious diseases. A substantial number of pilgrims to Hajj and Umrah are Turkish citizens (456,000 in 2014) but data are lacking on scale of the problem. We did a retrospective cross-sectional multicenter study in Turkey to explore the range of infections among inpatients who had recently returned from the Arabian Peninsula. Our inclusion criteria were patients who

had acquired an infection during their trip to an Arabian Peninsula country, or who became symptomatic within 1 week of their return. The data were collected retrospectively for January 1, 2013 and March 1, 2015. 185 Turkish patients were recruited to the study across 15 referral centers with travel associated infectious diseases after returning from Arabian Peninsula countries (predominantly Saudi Arabia 163 [88.1 %] for religious purposes 162 [87.5 %]). Seventy four (40.0 %) of them were ≥ 65 years old with numerous

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comorbidities including diabetes (24.3 %) and COPD (14.1 %). The most common clinical diagnosis was respiratory tract infections (169 [91.5 %]), followed by diarrheal diseases (13 [7 %]), and there was one case of MERS-CoV. Patients spent a median of 5 (3–7) days as hospital inpatients and overall mortality was 1.1 %. Returning travellers from the Arabian Peninsula present as inpatients with a broad range of infectious diseases similar to common community acquired infections frequently seen in daily medical practices in Turkey.

Introduction

It is a common occurrence for travellers to return home with febrile diseases [1]. In the majority of cases these infections are mild and self-limiting; however, approximately 8 % of all returning travellers present to hospitals during their trip or on their return home [2, 3]. Among these patients, approximately 3 % are subsequently unable to work on their return for an average of 2 weeks [3]. The distribution of infectious diseases is directly interrelated to the epidemiology of infections of the geographical area visited. Hence, mass gatherings pooling people from different parts of the world may impose serious risks for the acquisition and dissemination of infectious diseases [4].

One of the largest mass movements of travellers occurring each year is to Mecca for Hajj, when 2 million Muslim pilgrims travel to Saudi Arabia on the Arabian Peninsula from 184 countries [4, 5]. This journey is taken at a certain time of the year and according to Islamic belief must be carried out by every Muslim at least once during their lifetime. A substantial number of pilgrims are Turkish citizens: in 2014, 56,000 Muslim pilgrims from Turkey travelled to Mecca, in addition to 400,000 Turkish citizens who travelled to Umrah to visit various holy places [6]. There is also considerable travel between Turkey and other countries in the Arabian Peninsula (Bahrain, Kuwait, Qatar, Oman, South Iraq, South Jordan, United Arab Emirates, and Yemen). Travel to the Arabian Peninsula for Turkish people can basically be divided into religious and non-religious categories. Considering religious travel as with all mass gatherings of this nature, key public health concerns include gastrointestinal infections, tuberculosis, and influenza [4, 7]. In addition, in Saudi Arabia, *Aedes*, *Anopheles*, and *Culex* spp mosquitoes are present [4], and more recently the emergence of infections including Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection. Previous studies have reported multidrug resistant *Salmonella* strains [7] and nasal *Staphylococcus aureus* carriage [8] among Hajj pilgrims. However, data are lacking in the literature on travel-associated infections in returning travellers from the Arabian Peninsula to Turkey, and their impact on the Turkish health-care system.

In this multi-center study, therefore, we aim to describe the range of infections, clinical features, and scale of the problem

among in-patients hospitalized for an infectious disease in Turkey who have recently returned from the Arabian Peninsula.

Materials and methods

Study design

We carried out a retrospective cross-sectional multi-center study among Turkish in-patients with a diagnosis of a travel-associated infection leading to hospitalization after returning from the Arabian Peninsula countries (Bahrain, Kuwait, Qatar, Oman, Saudi Arabia, South Iraq, South Jordan, United Arab Emirates, and Yemen). Our inclusion criteria were adult patients (age over 15) who had acquired an infection during their trip to an Arabian Peninsula country, or who became symptomatic within 1 week of their return. Data were collected retrospectively between January 1, 2013 and March 1, 2015 across 15 Turkish referral centers with infectious diseases departments located in the main cities depicted in Fig. 1. We provided the definitions of infections in this study according to a pilot analysis preceding the study. The study was approved by the local ethics committee.

Clinical and laboratory analysis and follow-up

A detailed personal and travel history was obtained from all patients on admission to hospital, as per routine practice. All patients reporting recent travel to a country in the Arabian Peninsula, and who met study inclusion criteria, were recruited to the study and then assessed by study physicians on admission and daily during their hospitalization.

Microbiological cultures, including two sets of blood, throat, sputum or bronchoalveolar lavage and stool cultures were taken on admission. Routine biochemical analysis was done for all patients, and additional chest X-rays were done for patients with respiratory symptoms. Patients were questioned about their pulmonary symptoms including cough, expectoration, chest pain, and dyspnea. If abnormal pulmonary findings were present, patients underwent thoracic computerized tomography (CT).

For patients with fever (≥ 38 °C) and pneumonia or acute respiratory distress syndrome and/or cough, shortness of breath and the patients with influenza-like illness (ILI) including fever, malaise, headache, myalgia, and at least one of the three respiratory symptoms including cough, sore throat, and shortness of breath were further evaluated for MERS-CoV infection and influenza, respectively [9, 10]. These patients were additionally evaluated for parainfluenza virus (type 1, 2, and 3), coronavirus, adenovirus, enterovirus, parechovirus, human metapneumovirus, human baculovirus, respiratory syncytial virus (RSV) subtypes of A and B, and rhinovirus.



Fig. 1 The map showing the participating referral hospitals

When necessary patients were admitted to the intensive care unit (ICU) either for mechanical ventilation or because they were judged to be in an unstable condition requiring intensive care. Patients compatible with findings for Brucellosis were tested for the disease with serological tests [11].

Definitions

Upper respiratory tract infection An acute infection that includes tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, and the common cold [12].

Community-acquired pneumonia (CAP) Pneumonia was defined as a new infiltrate on the chest roentgenogram of two out of six clinical signs of pneumonia: cough, production of sputum, signs of consolidation on respiratory auscultation, temperature $>38\text{ }^{\circ}\text{C}$ or $<35\text{ }^{\circ}\text{C}$, leukocytosis [white blood cell count (WBC) $>10 \times 10^9/\text{l}$] or leukopenia (WBC $<4 \times 10^9/\text{l}$), and more than 10 % rods [13]. CAP is defined as pneumonia acquired outside of hospitals or a long-term care facility, and “atypical pneumonia” was defined as bilateral, more diffuse infiltrates on the chest X-ray examination of a pneumonia patient [14].

Acute tracheobronchitis A patient with dry cough and/or low-grade of fever ($<38\text{ }^{\circ}\text{C}$), sub-sternal pain, and fatigue in the absence of opacities on chest X-ray.

Acute exacerbation of chronic obstructive pulmonary disease (COPD) Association with increased frequency and severity of coughing and/or shortness of breath and wheezing, increased amount of sputum production, and/or a change in appearance of sputum in a patient with COPD.

MERS-CoV infection A confirmed case is a person with laboratory confirmation of MERS-CoV infection. Confirmatory laboratory testing requires a positive PCR on at least two specific genomic targets or a single positive target with sequencing on a second. A probable case is a patient under investigation with absent or inconclusive laboratory results for MERS-CoV infection [15].

Diarrhea Defined as the passage of three or more loose or liquid stools per day or more frequent passage than is normal for the individual.

Brucellosis Clinical findings in accordance with the disease, positive Rose-Bengal or Wright’s standard tube agglutination (STA) test titer of 1:160 or higher, and/or isolation of *Brucella* spp from body fluids. According to the duration of symptoms, brucellosis was classified as acute (<8 weeks), subacute (8–52 weeks), and chronic (>52 weeks) [11].

Co-morbid diseases Coexistent medical problems were retrieved according to the patients’ history recorded in their files in the hospitals.

Microbiological and serological investigations

Blood culture specimens were cultured by automatic systems, mainly by the BACTEC 9240 system (Becton-Dickinson, Maryland, USA). Blood samples were inoculated into the BACTEC system for a minimum of 7 days. Clinical specimens other than blood including sputum were inoculated onto sheep blood agar and chocolate agar, throat cultures were inoculated onto sheep blood agar, and stool cultures were inoculated onto eosin-methylene-blue (EMB) and Salmonella-

Shigella (SS) agar. Isolated microorganisms were defined according to standard microbiological techniques. *Brucella abortus* S99 antigen obtained from Pendik Animal Diseases Research Institute (Istanbul, Turkey) was used for the agglutination tests.

Molecular investigations

Multiplex PCR was used to test for MERS-CoV, RSV A-B, influenza virus, parainfluenza virus, adenovirus, coronavirus, rhinovirus, metapneumovirus, bocavirus, and enterovirus. Real-time PCR was done for MERS-CoV, parainfluenza virus type 1, 2, and 3, coronavirus, adenovirus, enterovirus, parechovirus, H1N1, influenza virus A-B, human metapneumovirus, parainfluenza virus, human bocavirus, RSV A-B, and rhinovirus.

Data collection and statistical methods

A standardized questionnaire was used to collect patients' data from participant centers. Data on demographics, travel history, clinical and laboratory parameters, treatment data, length of hospital stay and ICU admission, and outcomes were inserted into an Excel file (Microsoft Excel, 2010). The data analysis was done with SPSS (SPSS, Windows V.16.0). Descriptive

statistics were presented as frequencies, percentages for categorical variables and as mean \pm standard deviation and median [interquartile range (IQR)] for continuous variables according to the results of normality test. Normality test was done by one-sample Kolmogorov-Smirnov test.

Results

A total of 185 Turkish patients were recruited to the study across 15 referral centers (100 females; 85 males) with travel associated infectious diseases after returning from Arabian Peninsula countries. Breakdown by country is as follows: Saudi Arabia ($n=163$, 88.1 %), South Iraq ($n=8$, 4.3 %), Kuwait ($n=4$, 2.2 %), Qatar ($n=3$, 1.6 %), United Arab Emirates ($n=3$, 1.6 %), South Jordan ($n=2$, 1.1 %), Bahrain ($n=1$, 0.5 %), and Yemen ($n=1$, 0.5 %). One hundred sixty-two (87.5 %) patients had been there for religious purposes (e.g., Hajj, Umrah). Mean (SD) age was 60.3 (± 12.9) years. Seventy four (40 %) of them were ≥ 65 years old. The most common clinical diagnosis among our cohort was respiratory tract infections (169; 91.5 %). Diarrheal syndromes were the second most common diagnosis (13; 7 %). Clinical diagnoses of hospitalized travellers returning from the Arabian Peninsula are presented in Table 1. Microbiological

Table 1 Clinical diagnoses of hospitalized travellers returning from the Arabian Peninsula (N = 185)

Diagnosis	Number of cases	Percent of total (%)
Infectious syndromes		
Respiratory tract infections	169	91.5
• Community-acquired pneumonia	70	41.4
• Upper respiratory tract infection	56	33.1
• Acute tracheobronchitis	23	13.6
• Atypical pneumonia ^a	15	8.9
• Acute exacerbation of COPD	5	3.0
Diarrheal syndromes	13	7.0
• Acute diarrhea, etiology unknown ^b	11	84.6
• Enteritis due to <i>Salmonella enteritidis</i>	1	7.7
• Colitis due to <i>Shigella</i> sp.	1	7.7
Cellulitis	2	1.1
Acute brucellosis	1 ^c	0.5
Timing of hospitalisation since the onset of symptoms		
• Started in Arabian Peninsula	115	62.2
Median (IQR) days of symptoms	3 (2–6)	
• Symptoms started after returning to Turkey	70	37.8
Median (IQR) days of symptoms	3.5 (2–7)	

COPD chronic obstructive pulmonary disease, IQR interquartile range

^a Primary influenza pneumonia (1 patient), MERS-CoV pneumonia (1 patient)

^b Includes acute unspecified diarrhea and gastroenteritis

^c This patient worked as a butcher during Hajj

analyses were performed in accordance with the clinical requirements. Table 2 shows the confirmed infectious agents and their clinical presentations. The distribution of comorbid diseases were as follows: Diabetes mellitus 45 (24.3 %), COPD 26 (14.1 %), hypertension 16 (8.6 %), coronary artery disease 14 (7.6 %), congestive heart failure 6 (3.2 %), malignancy 6 (3.2 %), cerebrovascular event sequelae 2 (1.1 %), immunosuppression 2 (1.1 %), rheumatic disease 2 (1.1 %), chronic liver disease 2 (1.1 %), chronic renal failure 1 (5.4 %).

Bacterial cultures Cultures were performed in 176 patients. Blood cultures yielded *Brucella* sp (1 patient), *Salmonella enteritidis* (1 patient) and *Streptococcus pneumoniae* (1 patient). Non-b type *Haemophilus influenzae* was cultured in two patients, as well as *Acinetobacter baumannii* (1 patient), and *Streptococcus pneumoniae* (1 patient) identified from sputum culture. Throat culture of a patient with tonsillitis and a stool culture taken from a patient with diarrhea yielded a group-A beta hemolytic streptococcus (GAS) and a *Shigella* sp, respectively.

Serological testing Serological analyses were performed in a total of 41 patients including MERS-CoV, cytomegalovirus, Epstein-Barr virus, anti-HIV1-2, hepatitis B virus (HBV), hepatitis A virus (HAV), hepatitis C virus (HCV), Wright's

STA test and Legionella urine antigen test. Wright's STA test was positive at a titer of 1:320 in a male patient with blood cultures positive for *Brucella* sp, and MERS-CoV serological test was positive in a male patient diagnosed as severe CAP who died after 4 days of admission to the ICU.

Molecular testing Molecular analyses were performed in 97 patients. Multiplex PCR was done in 25 nasopharyngeal samples and real-time PCR was done for 72 samples. 20 (10.8 %) patients were positive for the following: influenza A virus [H1N1 (4 patients), H3N2 (1), untyped (3)], influenza B (7), adenovirus (2), coronavirus (1), rhinovirus (1), and human bocavirus (1).

Treatment and follow-up Empirical antibiotic treatment was given to the patients preceding the diagnosis. CAP and atypical pneumonia were treated with various combinations of beta-lactams, beta-lactam/beta-lactamase inhibitory combinations, clarithromycin, and respiratory fluoroquinolones. Twenty-three (12.4 %) ILI patients received oseltamivir for 5–7 days. Subsequently, 15 out of 23 cases were confirmed as influenza infection. Two (15.4 %) of 13 patients with diarrheal syndrome were given oral fluoroquinolones. Two patients with acute tonsillitis received procaine penicillin therapy. Bacterial cellulitis cases (n=2) were treated with

Table 2 Confirmed infectious agents and their clinical presentations

Infectious agent	Total	Pneumonia	URTI	Enteritis	Colitis	Other
Influenza A						
• H1N1	4	3	1	(-)	(-)	(-)
• H3N2	1	1	(-)	(-)	(-)	(-)
• Untyped	3	(-)	3	(-)	(-)	(-)
Influenza B	7	5	2	(-)	(-)	(-)
Adenovirus	2	1	1	(-)	(-)	(-)
Coronavirus-43	1	1	(-)	(-)	(-)	(-)
Rhinovirus	1	1	(-)	(-)	(-)	(-)
Bocavirus	1	1	(-)	(-)	(-)	(-)
MERS-CoV ^a	1	1	(-)	(-)	(-)	(-)
Viral agents, subtotal	21	14	7	(-)	(-)	(-)
<i>S. pneumoniae</i>	2	2	(-)	(-)	(-)	(-)
<i>H. influenza</i> non type-b	2	2	(-)	(-)	(-)	(-)
<i>H. influenza</i> type-b	1	(-)	1	(-)	(-)	(-)
<i>S. pyogenes</i>	1	(-)	1	(-)	(-)	(-)
<i>S. enteritidis</i>	1	(-)	(-)	1	(-)	(-)
<i>Shigella</i> sp.	1	(-)	(-)	(-)	1	(-)
<i>Brucella</i> sp.	1	(-)	(-)	(-)	(-)	1
Bacterial agents, subtotal	9	4	2	1	1	(-)
Total	30	18	9	1	1	1

URTI Upper respiratory tract infection, MERS-CoV Middle East Respiratory Syndrome Coronavirus

^a Superinfected with *A. baumannii*

parenteral beta-lactam/beta-lactamase inhibitory combinations. One patient with acute brucellosis was treated with a combination of oral doxycycline (100 mg every 12 h) for a period of 6 weeks and intramuscular streptomycin (1 g every 24 h) for 21 days.

ICU support and outcomes Six (3.2 %) patients required admission to ICU, of whom 5 (83.3 %) had CAP (1 of them MERS-CoV pneumonia) and 1 had COPD exacerbation. Patients spent a median of 3.5 (IQR 1.5–12.3) days in ICU and/or 5 (3–7) days as hospital in-patients. At the end of the study period, there were two deaths (a male patient with MERS-CoV and *A. baumannii* pneumonia, and a patient with atypical pneumonia). Overall mortality was 1.1 % for this cohort.

Discussion

Our study is the first attempt to explore the impact of extensive travel by Turkish citizens to the Arabian Peninsula and its impact on the Turkish health-care system in terms of the range and severity of infectious diseases acquired during travel in this region. A total of 169 (91.5 %) patients in our cohort presented with common community acquired infections frequently seen in daily medical practices in Turkey [16–18]. Patients in our cohort were diagnosed with a broad range of diseases, including diseases of key public health concern including MERS-CoV; respiratory tract infections predominated, followed by diarrheal disease/syndromes. In 115 (62.2 %) of the patients in our study symptoms started during their trip; in 70 (37.8 %), symptoms began when they returned home to Turkey. One hundred sixty-two (87.5 %) of the patients admitted to infectious diseases departments after returning from the Arabian subcontinent had been there for religious purposes. Three percent of recruited patients were admitted to the ICU and the overall mortality was low (1 %).

An official Turkish Hajj and Umrah report discloses that 37.4 % of Turkish citizens attending Hajj and Umrah are over 60 years of age [19]. In accordance with this statistic, 40 % of returning travellers hospitalized in Turkish hospitals were elderly patients over the age of 65 years in this study. In addition, 45 (24.3 %) of 185 patients we recruited had diabetes and 26 (14.1 %) had COPD, both of which are known to facilitate infections [20, 21]. An older age and the presence of comorbid conditions may have the potential to increase the severity of infections [22].

Respiratory tract infections predominated in our cohort, which concurs with preliminary French data indicating a high prevalence of cough (80 % of patients) both during Hajj and half remaining symptomatic on their returns [23]. Diarrheal syndromes were present in 13 (7 %) of our cohort. Poor food hygiene, water shortage, asymptomatic carriers among the

pilgrims, and poorly-stored meals are known to be the major reasons of diarrheal illnesses during the Hajj [24]. Hence, in this part of the world, these two groups of communicable diseases should be taken into consideration in returning travellers, and the responsible causative agents may differ according to the region/area that the individual many have travelled.

One study found that 11 % of patients were detected to have ILI during the 2013 Hajj season in Saudi Arabia itself. The viral causative agents were rhinovirus (25 %), influenza A virus (4 %), adenovirus (2 %), human coronavirus OC43/229E (2 %), parainfluenza virus-3 (2 %), parainfluenza virus-1 (1 %), and dual infections (2 %) [25]. In this study, in one-tenth of all cases molecular analyses disclosed the presence of viral causative agents. Fifteen (8.1 %) of the PCR positive viral respiratory tract infection patients were related to influenza (53.3 % influenza A viruses and 46.7 % influenza B viruses). The basic reason for this difference between the pilgrims in Mecca and those who returned to Turkey may be that influenza is more likely to result in hospitalizations compared to other viral upper respiratory tract infections [26] and our study group included only the hospitalized infection patients. It appears that ILI decreases among Hajj pilgrims as the vaccine coverage increases [27]. In Turkey, meningococcal vaccination for the pilgrims is mandatory while influenza vaccination, which is essentially included in the travel expenses, is provided to all pilgrims. However, there is still debate on the compliance of influenza vaccination in this population.

According to our data, one case with MERS-CoV overlapped by *A. baumannii* as an infection agent had died in the ICU indicating the potential transmission of infectious agents during travel. MERS-CoV was originally detected in Jeddah, Saudi Arabia in September 2012 [28]. Subsequently, MERS-CoV was reported to result in sporadic cases, healthcare associated outbreaks or intra-familial clusters in Saudi Arabia [29–31]. Afterwards, MERS-CoV cases were reported from Qatar, Jordan, United Kingdom, Germany, France, Tunisia, United Arab Emirates, and Italy [32]. MERS-CoV has been reported to impose a low public health risk for people either returning from the Hajj [33–35] or during the Hajj [25]. It appears that although MERS-CoV is not a widespread problem among the returning travellers of the Arabian Peninsula, it may result in morbidity or mortality for those affected.

The scale of travel that we are now witnessing from Turkey to the Arabian continent, particularly in older age-groups with co-morbidities that make them more prone to infectious diseases, means that returning travellers have noteworthy implications for the health system. Enhanced education around travel-related infections should be integrated to medical training curricula particularly for the emergent pathogens the clinicians are unfamiliar with. Countries with Muslim populations should principally be aware of the dynamic epidemiology in the Arabian continent in managing returning travellers.

Compliance with ethical standards**Funding** None to declare**Conflict of interest** The authors declare they have no competing interests.**Ethical approval** The study was approved by the local ethics committee.**Informed consent** Not applicable due to retrospective nature of the study.**References**

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