

Undiagnosed Active Pulmonary Tuberculosis among Pilgrims during the 2015 Hajj Mass Gathering: A Prospective Cross-sectional Study

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Abstract. Mass gatherings pose a risk for tuberculosis (TB) transmission and reactivation of latent TB infection. The annual Hajj pilgrimage attracts 2 million pilgrims many from high TB-endemic countries. We evaluated the burden of undiagnosed active pulmonary TB in pilgrims attending the 2015 Hajj mass gathering. We conducted a prospective cross-sectional study in Mecca, Kingdom of Saudi Arabia, for nonhospitalized adult pilgrims from five high TB-endemic countries. Enrollment criteria were the presence of a cough and the ability to produce a sputum sample. Sputum samples were processed using the Xpert MTB-RIF assay. Data were analyzed for drug-resistant TB, risk factors, and comorbidities by the country of origin. Of 1,164 consenting pilgrims enrolled from five countries: Afghanistan (316), Bangladesh (222), Nigeria (176), Pakistan (302), and South Africa (148), laboratory results were available for 1,063 (91.3%). The mean age of pilgrims was 54.5 (range = 18–94 years) with a male to female ratio of 2.6:1; 27.7% had an underlying comorbidity, with hypertension and diabetes being the most common, 20% were smokers, and 2.8% gave a history of previous TB treatment. Fifteen pilgrims (1.4%) had active previously undiagnosed drug-sensitive pulmonary TB (Afghanistan [12; 80%], Pakistan [2; 13.3%], and Nigeria [1; 6.7%]). No multidrug-resistant TB cases were detected. Pilgrims from high TB-endemic Asian and African countries with undiagnosed active pulmonary TB pose a risk to other pilgrims from over 180 countries. Further studies are required to define the scale of the TB problem during the Hajj mass gathering and the development of proactive screening, treatment and prevention guidelines.

INTRODUCTION

Tuberculosis (TB) remains a global public health problem with significant morbidity and mortality. In 2015, the World Health Organisation (WHO) estimated that 10.4 million people developed active TB of whom 480,000 developed multidrug-resistant TB (MDR-TB) with additional 100,000 cases of rifampicin-resistant TB (RR-TB).¹ Mortality from TB in 2015 reached 1.8 million, making it one of the top ten causes of death worldwide.^{1,2}

International travel, mass gathering events, and migration facilitate the spread of TB. In this context, the Kingdom of Saudi Arabia (KSA) is particularly relevant because of its hosting of the Hajj, where annually around 2 million pilgrims from over 180 countries visit KSA. Many of these pilgrims are elderly, have underlying health conditions, and originate from high TB-endemic countries. Living together in close proximity during the Hajj may facilitate TB transmission including TB from pilgrims with active pulmonary TB.³ There is a large burden of undiagnosed TB in high TB-endemic countries.¹ Pilgrims are not screened for TB before entry into the KSA, and it is likely that some may enter the Kingdom with active TB. Because respiratory tract infections and cough are common among pilgrims,⁴ patients are often diagnosed with upper respiratory tract infections and only those requiring hospitalisation may be thoroughly investigated.³ Pilgrims infected during Hajj may also spread the infection to contacts in their countries including potential MDR strains.

Scanty data are available on the prevalence of active TB during Hajj, and there have been no specific studies to define

the burden of TB during the pilgrimage.² Evidence of TB in pilgrims comes from clinical studies of causes of hospital admissions during Hajj which reported the isolation of *Mycobacterium tuberculosis* from 5% to 28% of patients with pneumonia during the event.^{2,5} Given the short duration of the Hajj pilgrimage, these active TB cases are likely to be either imported or reactivated.³ We conducted a cross-sectional study to evaluate the burden of undiagnosed active pulmonary TB in pilgrims arriving in the KSA for the 2015 Hajj.

MATERIALS AND METHODS

Study population and setting. The study was a prospective cross-sectional design study conducted in Mecca, KSA, over a 2-week period from September 14 to 29, 2015 (1–15 Dhul Hijja 1436H in the Islamic calendar). The study enrolled 1,164 consenting nonhospitalized adult pilgrims (> 18 years of age) who had cough and could voluntarily produce sputum samples. Pilgrims were selected from five countries in Africa and South Asia and chosen because they are endemic to TB, have high MDR/RR-TB rates, and large pilgrims' population (Table 1).

Data and samples collection. Pilgrims were enrolled at their place of residence during the Hajj. Face to face interviews and review of pilgrims' entry documents were used to fill in study questionnaires designed to collect data regarding pilgrims' contact information, demographics, and TB risk factors. Sputum samples were collected in sterile containers from each pilgrim and maintained in cold conditions (2–8°C) until storage at –80°C for later processing.

Samples processing. All sputum samples were processed after Hajj at the Saudi National TB Laboratory (Riyadh, KSA) using the WHO-endorsed Xpert MTB/RIF assay for the rapid diagnosis of TB and MDR-TB as described previously.⁶

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TABLE 1
Target countries from which pilgrims were enrolled

Country	TB endemicity* incidence/100,000 population	Prevalence of MDR/RR-TB* (% among new cases)	Estimated number of Hajj pilgrims in 2015
South Asia			
Afghanistan	189	3.9	25,037
Bangladesh	225	1.6	102,795
Pakistan	270	4.2	160,611
Africa			
Nigeria	322	4.3	75,212
South Africa	834	3.5	2,435

RR-TB = rifampicin-resistant tuberculosis (TB); MDR-TB = multidrug-resistant TB.
* 2015 data (www.who.int/tb/data).

Data analysis. Characteristics of the study population were summarized as frequencies and percentages for qualitative variables and as means, range, and standard deviations (SDs) for quantitative variables. The association between demographic variables and TB was evaluated by χ^2 test or Fisher's exact test as appropriate. In addition, odds ratios (ORs) and their CIs were calculated. Multiple logistic regression analysis, using penalized likelihood (Firth method), was performed to examine the potential impact of the variables that were identified as being significant with $P \leq 0.1$ in the univariate analysis. A Stata ado program written by Coveney (2015) was used to fit the multiple logistic regression model. All other tests for significance were two-sided and P values < 0.05 were considered statistically significant. All analyses were done using the SPSS 22.0 (SPSS Inc., Chicago, IL) software program.

Ethics approval and consent to participate. The study was approved by the King Fahad Medical City Ethics Committee and the Institutional Review Board. All participants gave verbal consent before enrolment, and the study was conducted in accordance with the Ethics Committee's guidelines.

RESULTS

The study enrolled 1,164 pilgrims originating from five TB-endemic countries in Africa and South Asia (Table 1). The characteristics of the study population are summarized in Table 2. The mean age of pilgrims was 54.5 (SD = 12.1 years, range = 18–94 years) with a male to female ratio of 2.6:1. Over half of the respondents had no formal education, and 27.7% declared having an underlying health condition. Hypertension and diabetes were the most common comorbidities (Table 3).

A fifth of the respondents declared that they had smoked or were current smokers of tobacco products such as cigarettes, cigars, or pipes, and 5.7% had occupations associated with increased risk of TB infection (Table 2). Travel information indicated that 183 (16.2%) respondents have traveled outside their country of residence in the previous year visiting countries in Africa, Asia, the Middle East, Europe, and North America. The most common destinations visited were Pakistan (50.2%), India (13.1%), KSA (8.7%), Malaysia (5.0%), UK (4.4%), and France (4.4%). While no pilgrim declared that they were receiving TB treatment at the time of enrolment, 31 (2.8%) revealed that they had been treated for TB in the past, all of whom confirmed that they had completed their TB treatment. The latter ranged in duration from 2 to 4 months, which is shorter than the standard treatment duration for TB,

TABLE 2
Demographic characteristics of the enrolled pilgrims' population

Variable	Number (n)	Percentage (%)
Pilgrims enrolled	1,164	–
Gender	1,140	–
Male	823	72.2
Female	317	27.8
Age	1,106	–
Mean (range)	54.5 (18–94)	–
≤ 47	302	27.3
> 47 –55	275	24.9
> 55 –64	296	26.8
> 64	233	21.1
Country of residence	1,164	–
Afghanistan	316	27.1
Bangladesh	222	19.1
Nigeria	176	15.1
Pakistan	302	25.9
South Africa	148	12.7
Level of education	1,155	–
No formal education	597	51.7
Primary education	163	14.1
Secondary education	217	18.8
University-higher education	178	15.4
Occupation	1,130	–
Health care worker	34	3.0
Miner	2	0.2
Laboratory personnel	14	1.2
Refugee camp worker	7	0.6
Prison staff	7	0.6
None of the above	1,066	94.3
Underlying health conditions	1,069	–
Yes	296	27.7
No	773	72.3
Pregnancy	1,036	–
Yes	1	0.01
No	1,035	99.9
Tobacco smoker (currently or in the past)	1,145	–
Yes	224	19.6
No	921	80.4
Travel outside current country of residence in the past year	1,129	–
Yes	183	16.2
No	946	83.8
Recently (past month) lived in a household with an adult with a cough	1,145	–
Yes	138	12.0
No	1,007	88.0
Any of close contacts ever diagnosed or treated for TB	1,149	–
Yes	57	5.0
No	768	66.8
Unsure	324	28.2
Currently coughing up blood	1,150	–
Yes	33	2.8
No	1,117	97.2
Ever been treated for TB	1,124	–
Yes	31	2.8
No	961	85.5
Unsure	132	11.7
Currently receiving TB treatment	957	–
Yes	0	0.0
No	957	100

TB = tuberculosis.

and may affect persistence of the disease and risk for MDR-TB. The majority (84%) of those previously treated for TB originated from Bangladesh.

Xpert MTB/RIF assay results were available for 1,063 (91.3%) of the samples, 15 (1.4%) of which were positive for TB. No rifampicin resistance was detected in any of the

TABLE 3
Underlying health conditions among enrolled pilgrims

Underlying health conditions	N = 296	Percentage (%)
Hypertension	174	58.8
Diabetes	125	42.2
Chronic kidney disease	6	2.0
Chronic lung disease	13	4.4
Chronic liver disease	7	2.4
Cardiovascular disease	47	15.9
Stroke	1	0.3
Cancer	2	0.7
Immunosuppressive illness	0	0.0
Other	36	12.1

positive samples, hence by proxy no MDR-TB was detected. The characteristics of pilgrims with positive TB are summarized in Table 4. Most originated from Afghanistan (12, 80%), were male (10, 66.6%) and had no formal education (13, 86.6%). Their age ranged from 44 to 74 years old and they had spent 7–23 days in the KSA at the time of enrolment in the study. Four pilgrims (26.6%) traveled to Pakistan in the previous year, five (33.3%) declared having an underlying health condition but none worked in one of the TB risk occupations in the survey. There were no current tobacco smokers among the TB cases but two (13.3%) had smoked such products in the past. None of the TB-positive pilgrims declared having a history of TB themselves or in a close contact.

The result of the univariate analysis showing the association between TB and demographic variables are summarized in Table 5 and reveal that only education showed a statistically significant association ($P = 0.01$). Pilgrims with no formal education were over six times more likely to be TB positive compared with those with some form of education (primary, secondary, or higher education) [(OR = 6.17; 95% CI = 1.38–27.4)]. The prevalence of active TB was lowest among the youngest age group (≤ 47 year old) and increased with age. TB prevalence was higher among females, pilgrims residing in South Asia, those with underlying health conditions, and those who traveled outside their current country of residency in the previous year, but the association was not statistically significant for any of these factors. Similarly, no significant association was found between tobacco smoking or recently living in the same household as an adult with cough and TB.

Only variables found to be significant at the 1% level in the univariate analysis (geographic area of residency and education) were considered as candidates for the multiple logistic regression analysis. Penalized likelihood (Firth method) was used for the fitting of the logistic regression as the maximum likelihood estimation of the logistic regression was not appropriate for our study with such a small number of events. The results indicated that only education was marginally significant after adjusting for geographic area of residency ($P = 0.052$) and that pilgrims with no formal education were nearly four times more likely to develop active TB than those with some form of education (adjusted OR = 3.9; 95% CI = 0.98–16.0).

DISCUSSION

Pilgrims attending Hajj maybe at a risk of acquiring TB infection.⁷ Our study is the first to screen Hajj pilgrims with

productive cough for undiagnosed pulmonary TB and has several important findings. We found that 1.4% of Hajj pilgrims with cough from TB-endemic countries had undiagnosed active TB. This prevalence is within the range found among migrants to low-incidence countries (0.1–10%),⁸ yet it means that potentially 14 out of each 1,000 pilgrims from TB-endemic countries symptomatic for cough could have active TB during Hajj. This is concerning given that the estimated total number of pilgrims attending the 2015 Hajj from the WHO's top 20 TB burden countries was 1,450,000, and the prevalence of cough among Hajj pilgrims can reach 80%.⁴ Considering the short time pilgrims spent in KSA at the time of enrolment in the study, it is likely that the identified active TB cases are imported or reactivation of latent TB infection.³

During the 2015 Hajj season, 44 cases of TB among pilgrims and residents were diagnosed in Mecca hospitals. We detected active TB among pilgrims symptomatic for cough but not seriously ill to be hospitalized or require medical attention and therefore not diagnosed. This is in accordance with previous TB prevalence surveys which have shown that an important proportion of infectious individuals with bacteriologically positive sputum do not experience symptoms or symptoms of sufficient severity to prompt health-seeking behavior.^{9–11} Also, screening only individuals who meet the TB screening criteria of cough over 2 or 3 weeks may result in a sizable proportion of active TB cases to be missed.

Most (80%) TB cases detected in the study were in pilgrims from Afghanistan and none were from South Africa. This is surprising given that among the countries included in the study, Afghanistan has the lowest TB burden and South African has nearly 4.5 times its TB incidence rate.¹ Afghanistan is one of the poorest countries in the world with some of the lowest indicators of socioeconomic and human development indices ratings. As a consequence, health services coverage and delivery, including TB services, may be limited resulting in TB cases being not diagnosed, notified, treated, or in these processes being delayed which leads to persistent transmission.^{1,12} In addition, underreporting of TB cases from the country may also be a factor. The epidemiology of TB in South Africa is closely related to that of the human immunodeficiency virus (HIV).¹³ Most of the Muslim population in South Africa are of Asian (mostly Indian) descent which represent around only 2.5% of the population.¹⁴ The difference in the socioeconomic status, behavioural factors, and lower prevalence of HIV among this ethnic group may also explain the results observed in our study.^{14,15}

Education was strongly associated with TB prevalence and pilgrims with no formal education were four times more likely to have TB. TB is associated with socioeconomic status of which education is one indicator. Individuals with low socioeconomic status, including low or no education, have higher TB risk and prevalence, are less likely to seek medical care, have longer diagnosis delay time, and are at higher risk of death from TB.^{16,17} Populations with little or no education are generally disadvantaged from a social, geographic, or economical point of view, all factors that are associated with TB morbidity and mortality.¹⁶ In addition, low education is associated with poor knowledge of TB and attitude to the disease, which can facilitate transmission and can lead to delaying health-seeking behavior, lack of adherence to treatment regimes, treatment failure and disease complications, and death.¹⁸

TABLE 4
Characteristics of the tuberculosis-positive pilgrims

Pilgrim	Country of residence	Age	Gender	Time in KSA (days)	Highest level of education	At risk occupation*	Country traveled to in the last year	Tobacco smoker	Underlying health condition(s)	Previously treated for TB	Currently coughing up blood	Recently (past month) lived in a household with an adult with a cough	Any of close contacts or colleagues or treated for TB	Rifampicin resistance
1	Nigeria	50	F	10	NFE	No	None	Never	None	No	No	ND	No	No
2	Pakistan	44	F	7	SE	No	None	Never	None	No	No	Yes	No	No
3	Pakistan	57	M	7	NFE	No	None	Never	None	No	No	No	Unsure	No
4	Afghanistan	ND	F	23	NFE	No	None	Never	Hypertension	Unsure	No	No	No	No
5	Afghanistan	54	F	14	NFE	No	Pakistan	Never	ND	No	No	No	No	No
6	Afghanistan	65	F	12	NFE	No	None	Never	CLD	No	No	No	No	No
7	Afghanistan	74	M	21	NFE	No	None	Never	ND	No	No	No	No	No
8	Afghanistan	49	M	19	NFE	No	None	Never	ND	No	No	No	No	No
9	Afghanistan	57	M	15	NFE	No	Pakistan	Never	Diabetes	No	No	No	No	No
10	Afghanistan	58	M	12	NFE	No	Pakistan	Past	Hypertension	No	No	No	No	No
11	Afghanistan	63	M	11	NFE	ND	Pakistan	Past	Diabetes	No	No	No	Unsure	No
12	Afghanistan	50	M	9	SE	No	None	Never	ND	No	No	No	No	No
13	Afghanistan	68	M	9	NFE	No	None	Never	None	No	No	No	No	No
14	Afghanistan	67	M	9	NFE	No	None	Never	None	No	No	No	No	No
15	Afghanistan	63	M	8	NFE	No	None	Never	None	No	No	No	No	No

KSA = Kingdom of Saudi Arabia; F = female; M = male; NFE = no formal education; SE = secondary education; ND = not determine; CLD = chronic lung disease.
*Health care worker, miner, laboratory personnel, refugee camp worker, prison staff.

Worldwide, TB is more prevalent in males than females, and males tend to have higher prevalence of undiagnosed TB than females.^{1,9} This is contrary to the results in our study. A possible explanation for this observation is that most (14/15) of the TB cases in our study were from Afghanistan or Pakistan, where the prevalence of TB is reported to be higher among females.^{1,19} The reported male:female TB ratio in Afghanistan, where most of our identified cases came from, is 0.7¹, which is similar to the ratio found in our study.

Underlying health conditions were present among a sizable number of pilgrims with hypertension and diabetes being the most common conditions. This is in accordance with other surveys conducted among Hajj pilgrims.^{4,20} Although not statistically significant, we found that pilgrims with underlying health conditions were twice more likely to have TB. Non-communicable diseases are risk factors for TB,²¹ and there is a growing awareness of the influence of TB comorbidity with these conditions as well as the burden of unsuspected TB.²² The management of noncommunicable disease is essential to reduce the burden of these diseases during Hajj and could avoid a significant number of TB cases and related deaths.²³ As such, the WHO has incorporated the management of noncommunicable diseases into its End-TB strategy.²⁴

Extremes of age are also risk factors for TB.²¹ Prevalence of TB in our study increased with age which is in accordance with other TB surveys.^{1,10,11} We found that pilgrims aged over 64 years were 5.3 times more likely to be TB positive than those aged 47 years old or less. This is significant given that elderly pilgrims represent a sizable proportion of the Hajj population (roughly 25% are at least 65 years old) and that TB has been mainly reported in elderly pilgrims during the event.^{5,25}

We found no significant association between tobacco smoking and TB. This is in contrast with the strong evidence that smoking, active or passive, is significantly associated with increased risks of TB infection and disease, TB transmission, TB mortality, and recurrent TB.^{26,27} Smoking also influences the clinical manifestations and outcomes of TB adversely affecting baseline disease severity, bacteriological response, treatment outcome, and relapse in TB and leading to a faster and more severe progression to TB.²⁷

The results of our study highlight the need for more attention toward TB and its burden during Hajj, including formulation of appropriate policies and interventions to prevent infection and transmission. Such interventions may include increase in education and awareness regarding TB and its prevention among pilgrims through targeted campaigns to encourage health-seeking behavior in case of symptoms and adherence to treatment and to general infection prevention measures. There may also be a need for a pre-Hajj TB screening for pilgrims from certain endemic countries to prevent TB importation by prompt detection of cases and initiation of effective treatment before arrival to the KSA. Although under a different context, TB screening programs are already in effect in a number of high-income and low-TB incidence countries as pre-entry requirements for immigrants and were shown to have the highest impact and be most cost effective if they are targeted toward arrivals from high TB-endemic countries.⁸ TB screening for prevention and control is also implemented in refugee situations and among displaced populations.²⁸

The introduction of such screening programs for Hajj pilgrims will require further research and considerations into the target countries as well as to the practicalities, benefits, and

TABLE 5
Association between tuberculosis and demographic variables

Variable	n	TB+ve	%	OR (95% CI)	P
Gender	–	–	–	–	0.68
Female	289	5	1.73	1	–
Male	752	10	1.33	0.76 (0.25, 2.25)	–
Age	–	–	–	–	0.48
≤ 47	273	1	0.37	1	–
> 47–55	258	4	1.55	4.28 (0.47, 38.5)	–
> 55–64	274	5	1.82	5.05 (0.58, 43.5)	–
> 64	208	4	1.92	5.33 (0.59, 48.0)	–
Geographic area of residence	–	–	–	–	0.09
Africa	304	1	0.33	1	–
South Asia	759	14	1.84	5.69 (0.74, 43.4)	–
Education	–	–	–	–	0.01
Primary or higher education	508	2	0.39	1	–
No formal education	546	13	2.38	6.17 (1.38, 27.4)	–
Underlying health conditions	–	–	–	–	0.20
No	704	6	0.85	1	–
Yes	273	5	1.83	2.17 (0.65, 7.17)	–
Tobacco smoker (currently or in the past)	–	–	–	–	0.54
Yes	205	2	0.98	1	–
No	839	13	1.55	0.62 (0.14, 2.79)	–
Traveled outside current country of residence in the past year	–	–	–	–	0.27
No	863	11	1.27	1	–
Yes	167	4	2.40	1.90 (0.59, 6.04)	–
Recently (past month) lived in a household with an adult with a cough	–	–	–	–	0.57
No	918	13	1.42	1	–
Yes	127	1	0.79	0.55 (0.07, 4.25)	–

cost of such undertakings. These include the establishment, management, and sustainability of such screening programs as well as the availability and accessibility to TB health services for those identified to have active TB. Given that most countries likely to require a pre-Hajj TB screening are also those with the lowest income and least developed infrastructures to manage and sustain such screening programs, international engagement and collaboration, funding, and investment will be required. Nevertheless, the development and deployment of new and rapid point-of-care molecular TB diagnostic technologies, which could be subsidized in low-income countries to reduce the cost,¹ would be most beneficial.

Our study has some limitations. We only screened 1,164 pilgrims from five countries which represent only a small proportion of the Hajj pilgrims' population. We did not include some countries with the largest number of Hajj pilgrims such as Indonesia and India as well as countries with the highest MDR-TB burden in the world such as the Russian Federation and many former Soviet Union countries¹ which also send pilgrims to Hajj. Finally, because of cultural and ethical considerations, our study did not collect data on the HIV status or on alcohol or substance abuse among pilgrims, which are established risk factors for TB.²¹

CONCLUSIONS

In summary, we found that a proportion of Hajj pilgrims have undiagnosed and untreated active TB which may represent an important source of transmission. In light of these results, further studies investigating TB during Hajj and the impact of this mass gathering on TB transmission and epidemiology worldwide are warranted. These investigations will help inform public health policies and direct interventions for the optimal

awareness, surveillance, screening, treatment and management, prevention, and control of TB during Hajj and other mass gatherings worldwide. TB prevention at Hajj is an important priority and will go a long way toward achieving the WHO's End-TB strategy goals.

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