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Tuberculosis and mass gatherings—opportunities for defining burden, transmission risk, and the optimal surveillance, prevention, and control measures at the annual Hajj pilgrimage[☆]

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SUMMARY

Tuberculosis (TB) is now the most common infectious cause of death worldwide. In 2014, an estimated 9.6 million people developed active TB. There were an estimated three million people with active TB including 360 000 with multidrug-resistant TB (MDR-TB) who were not diagnosed, and such people continue to fuel TB transmission in the community. Accurate data on the actual burden of TB and the transmission risk associated with mass gatherings are scarce and unreliable due to the small numbers studied and methodological issues. Every year, an estimated 10 million pilgrims from 184 countries travel to the Kingdom of Saudi Arabia (KSA) to perform the Hajj and Umrah pilgrimages. A large majority of pilgrims come from high TB burden and MDR-TB endemic areas and thus many may have undiagnosed active TB, sub-clinical TB, and latent TB infection. The Hajj pilgrimage provides unique opportunities for the KSA and the 184 countries from which pilgrims originate, to conduct high quality priority research studies on TB under the remit of the Global Centre for Mass Gatherings Medicine. Research opportunities are discussed, including those related to the definition of the TB burden, transmission risk, and the optimal surveillance, prevention, and control measures at the annual Hajj pilgrimage. The associated data are required to develop international recommendations and guidelines for TB management and control at mass gathering events.

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1. Introduction

Tuberculosis (TB) was declared a global emergency by the World Health Organization (WHO) in 1993.¹ The latest 2015 WHO Annual Global TB Report contains TB data that are of major concern

for all public health authorities.² In 2014, TB was responsible for 1.5 million deaths, making it the most common infectious cause of death worldwide. An estimated 9.6 million people developed active TB (5.4 million men, 3.2 million women, and 1.0 million children). Multidrug-resistant TB (MDR-TB) is now widespread with an estimated 480 000 cases. There were an estimated three million people with active TB including 360 000 with MDR-TB who were not diagnosed and remained untreated, continuing to fuel TB transmission in the community. The UN Sustainable Development Goals (SDGs) include ending the TB epidemic by 2030 as a specific goal.³ The WHO post-2015 End TB Strategy adopted by the World Health Assembly in May 2014,⁴ has two specific targets: (1) a 50%

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reduction in incidence and 75% reduction in mortality by 2025, and (2) an overall 90% reduction in incidence and 95% reduction in mortality by 2035.

The ease of international travel and migration are two of several factors that are responsible for the spread of TB across the world.^{5–8} Every year, millions of people travel to sporting^{9,10} and religious events,¹¹ where the mass gathering of people is conducive to the transmission of a range of infectious diseases, including TB.^{12,13} Developing an accurate evidence base to optimize surveillance, screening, transmission risk, treatment, prevention, and control measures for TB at mass gathering events is an important priority, and will go a long way towards achieving the WHO post-2015 End TB Strategy goals.⁴

2. Mass gatherings and TB transmission

When the FIFA World Cup Football event in 2010 was hosted by South Africa – a high TB and MDR-TB prevalence country – there was widespread concern among global public health authorities of the spread of TB between attendees and the exportation of MDR-TB outside South Africa.^{14,15} There is no existing global consensus or scientific evidence base for the most effective public health measures to reduce TB transmission at mass gathering events, either within the host country or in the countries from which the attendees originate. These data are required to develop optimal TB surveillance, screening, treatment, prevention, and control measures for mass gathering events, to protect the attendees and the local population of the host country.

Obtaining an accurate scientific evidence base on the burden of TB and risk of transmission at mass gatherings is difficult due to operational and logistical difficulties in conducting cross-sectional and longitudinal cohort studies. Furthermore, since TB is a chronic disease, clinical manifestations of new cases of active TB only become evident months after the mass gathering event. In light of the continuing global TB emergency,² it is important to define the burden of TB (active TB, sub-clinical TB, and latent TB infection (LTBI)), the transmission risk, and the transmission dynamics of drug-sensitive and drug-resistant *Mycobacterium tuberculosis* strains at mass gathering events.

Conducting research at mass gatherings requires effective collaboration between local organizers of the mass gathering event and international stakeholders. This should include making available the funding required to conduct a range of priority studies, examples of which are listed in Table 1. The collaboration should include the development of pre-specified protocols for research and logistics planning, and have close involvement with the WHO and national ministries of health. This collaborative approach will enable the provision of resources and infrastructure for screening and monitoring of large cohorts of travellers and local populations before travel, during the event, and after return home. It will also facilitate the translation of the evidence base into policy and practice and the publication of guidelines and recommendations.

3. Opportunities for conducting TB research at mass gatherings

The Global Centre for Mass Gatherings Medicine (GCMGM) has its headquarters at the Ministry of Health in Riyadh, Kingdom of Saudi Arabia (KSA), and is linked to a virtual network of other WHO collaborating centres for mass gatherings and academic and public health institutions.¹⁶ It provides a unique consortium of multidisciplinary expertise to conduct research on a range of public health issues and to gather the most appropriate evidence base for use by countries hosting mass gathering events. The formal discipline of Mass Gatherings Medicine was launched at the World Health Assembly of Ministers of Health in Geneva in May 2014.^{16,17} With

recent advances in technology, such as the availability of rapid screening tests for LTBI and active pulmonary TB and for the identification of drug-resistant strains of *M. tuberculosis*,^{18,19} unique opportunities now present for conducting TB research studies on cohorts of attendees at mass gatherings.

The KSA is particularly prone to the importation and exportation of TB because of the constant flow throughout the year of huge numbers of migrant workers and pilgrims from high TB burden countries. Every year, an estimated 10 million pilgrims from 184 countries travel to the holy cities of Makkah and Madinah in the KSA to perform the religious rites of the Hajj and Umrah pilgrimages.¹¹ A large majority of pilgrims come from high TB burden areas. In addition, two million pilgrims come from other regions of the KSA where TB and MDR-TB are important public health issues among both the immigrant and indigenous populations.^{20–25} Screening for TB or LTBI before entry into the KSA is not a visa prerequisite for pilgrims. Since many pilgrims come from high TB endemic countries,² it is likely that many pilgrims will have undiagnosed active TB, sub-clinical TB, or LTBI. If the KSA and the 184 countries from which the pilgrims originate are to achieve the WHO post-2015 End TB Strategy goals,⁴ it is important to define the burden of active TB and LTBI, the transmission risk to both pilgrims and KSA residents, and the transmission dynamics of drug-sensitive and drug-resistant *M. tuberculosis* strains. This scientific evidence base is required in order to develop optimal surveillance, screening, treatment, prevention, and control measures for pilgrims and the local resident population of the KSA.

4. Populations at risk of TB during the Hajj

A range of respiratory tract pathogens, including *M. tuberculosis* and microbes resistant to antibiotics, are transmitted during the Hajj pilgrimage.^{24–37} These are acquired by pilgrims during the unavoidable frequent close contact with crowds during travel, at points of entry, within living quarters, and whilst performing religious rites. *M. tuberculosis* is spread by the aerosol route by people with active pulmonary TB disease who cough or sneeze, and thus transmission can occur amongst several groups of people: (1) between pilgrims, (2) from pilgrims to KSA residents, (3) from KSA residents to pilgrims, and (4) from pilgrims to their local communities when they return to their home countries. Since pilgrims stay in the KSA for only a few weeks, and the period between first infection with *M. tuberculosis* and developing active TB disease is long, it is most likely that active TB disease diagnosed during Hajj is either imported by the pilgrim or is due to reactivation of LTBI. An estimated two billion people worldwide have asymptomatic LTBI, thus many pilgrims with LTBI could experience reactivation and progress rapidly to developing active TB disease because of risk factors that compromise their immune responses, such as stress, physical and mental exhaustion, old age, poor nutrition, co-morbidities such as diabetes and chronic pulmonary, liver, and renal diseases, immunosuppressive therapy, or other causes of immune-compromise.³⁸

5. TB prevalence in the holy cities

TB in the Makkah region (Jeddah, Makkah) is known to be an important public health problem affecting all residents, Saudis and non-Saudis. The cities have TB incidence rates up to four times the national KSA rate.²⁰ Community-based surveys using purified tuberculin antigen skin tests have shown more people with positive skin tests living in Makkah (20%) compared with other KSA regions (10%).³⁶ Accurate data on TB prevalence in pilgrims and their role in contributing to the higher TB rates in the Makkah region population are not available. Respiratory tract infections spread rapidly and almost all pilgrims develop the 'pilgrims

Table 1
Priority research studies for TB in pilgrims and KSA airport staff and healthcare workers in the Makkah region

Timing of study enrolment	Aim of study	Study design	Study population
Pre-Hajj departure	Study 1: To define the background burden of active pulmonary TB (both drug-sensitive and MDR-TB) in pilgrims	Cross-sectional study Enrolment: any pilgrim able to produce a sputum sample, irrespective of health status	Pilgrims of all ages from selected high TB and low TB burden countries
Pre-Hajj departure	Study 2: To define the background burden of active pulmonary TB (both drug-sensitive and MDR-TB) in Jeddah airport staff and KSA healthcare workers	Cross-sectional study Enrolment: any staff member able to produce a sputum sample, irrespective of health status	KSA staff selected from airport and Hajj health services
Pre-Hajj departure and post-Hajj follow-up	Study 3: To define the background burden of LTBI in pilgrims Study 4: To determine the acquisition of <i>Mycobacterium tuberculosis</i> infection or active TB during the Hajj period in pilgrims	(a) Cross-sectional study (b) Longitudinal follow-up study	Pilgrims: adults from selected (a) high TB burden countries, and (b) low TB burden countries
Pre-Hajj and post-Hajj follow-up	Study 5: (a) To define the background burden of LTBI in Jeddah airport staff and KSA healthcare workers Study 6: (b) To determine the acquisition of <i>M. tuberculosis</i> infection or active TB during the Hajj period in Jeddah airport staff and KSA healthcare workers	(a) Cross-sectional study (b) Longitudinal follow-up study	KSA staff selected from airport and Hajj health services
Pre-Hajj departure	Study 7: Knowledge, attitudes of TB, and knowledge of infection control practices of pilgrims	Descriptive cross-sectional study	Pilgrims of all ages from selected (a) high TB burden countries, and (b) low TB burden countries
Pre-Hajj	Study 8: Knowledge, attitudes of TB, and knowledge of infection control practices of KSA staff selected from airport and Hajj health services	Descriptive cross-sectional study	KSA staff selected from airport and Hajj health services
Pre-Hajj, during Hajj, and post-Hajj	Study 9: Educational intervention study of cough etiquette, infection control measures, plus wearing masks of pilgrims	Randomized longitudinal case controlled cohort study	Pilgrims of all ages from selected (a) high TB burden countries, and (b) low TB burden countries
Pre-Hajj, during Hajj, and post-Hajj	Study 10: Educational intervention study of cough etiquette, infection control measures, plus wearing masks of KSA staff selected from airport and Hajj health services	Randomized longitudinal case controlled cohort study	KSA staff selected from airport and Hajj health services
During Hajj	Study 11: DS-TB prevalence study in pilgrims in the community with respiratory symptoms	Cross-sectional study of pilgrims falling ill with RTIs	Pilgrims seeking healthcare for RTIs at clinics
During Hajj	Study 12: MDR-TB prevalence study in pilgrims in the community with respiratory symptoms	Cross-sectional study of pilgrims falling ill with RTIs	Pilgrims seeking healthcare for RTIs at clinics
During Hajj	Study 13: Proactive screening for TB and MDR-TB in pilgrims admitted to hospitals in Makkah irrespective of admission diagnosis	Cross-sectional study of pilgrims (a) on general wards, and (b) in the ITU	Pilgrims admitted to hospitals
During Hajj	Study 14: Proactive screening for TB and MDR-TB in healthcare workers admitted to hospitals in Makkah irrespective of admission diagnosis	Cross-sectional study of HCWs (a) on general wards, and (b) in the ITU	HCWs admitted to hospitals
During and after Hajj	Study 15: To define <i>M. tuberculosis</i> transmission patterns in the Makkah region during the Hajj period	Biobank of mycobacterial isolates from the Hajj studies analysed and compared with data from the home countries of pilgrims	Molecular and phylogenetic analyses of mycobacterial isolates

TB, tuberculosis; MDR, multidrug-resistant; KSA, Kingdom of Saudi Arabia; LTBI, latent tuberculosis infection; DS, drug-sensitive; RTI, respiratory tract infection; ITU, intensive therapy/care unit; HCW, healthcare worker.

cough.³⁰ Most pilgrims with a cough are assumed to have an acute upper or lower respiratory tract infection due to common viral or bacterial pathogens, and they are treated empirically and may not be proactively investigated for TB unless they are hospitalized. The majority of research studies that have been published have focused on the generic issue of acute bacterial and viral respiratory tract infections,^{25–35} since they are associated with significant morbidity, and some associated with a high mortality may have pandemic potential.^{25–27}

6. Available data on TB in pilgrims

There have been no specific large-scale controlled studies to ascertain the TB case load in pilgrims during the Hajj or Umrah. Evidence of TB in pilgrims comes from clinical studies of causes of hospital admissions during the Hajj. Alzeer et al. reported that of

46 hospitalized patients with pneumonia during the 1994 Hajj, 13 (28%) had confirmed TB.³⁷ Madani and colleagues performed a cross-sectional study of patients admitted to intensive care units (ICU) in hospitals at Mina and Arafat during the 2003 Hajj.³⁹ Pneumonia was found to be the most common cause of admission in the 808 patients (19.7%), and sputum culture-confirmed TB was diagnosed in 5.9% of patients. Mandourah et al. performed a prospective study of patients admitted to ICUs at 15 hospitals in Makkah and Madinah over two consecutive Hajj years, 2009 and 2010.⁴⁰ Of the 452 patients studied, pneumonia was the primary cause of critical illness in 123 (27.2%) and TB was diagnosed in 4.9%. The presence of seriously ill pilgrims with TB in hospitals probably represents the tip of the iceberg and indicates that a large number may remain undiagnosed. A prospective cohort study of pilgrims from Singapore showed them to be at high risk of exposure to *M. tuberculosis* infection during their stay in the KSA.⁴¹

Of 149 pilgrims who were QuantiFERON-TB assay negative prior to the Hajj, 15 (10%) showed significant positive responses at 3 months after their return to Singapore from Hajj. Whilst these results are subject to issues in interpretation due to several variables that affect the performance of the assay and the small numbers of pilgrims studied, the data highlight the risk of acquiring *M. tuberculosis* infection during the Hajj.

7. Defining the burden of TB and *M. tuberculosis* transmission risk in pilgrims and in KSA residents

The diagnosis and treatment of TB in pilgrims in the pre-Hajj preparation stage, during their travel, and after their return home from the pilgrimage, is a formidable challenge. Operational and logistical issues in TB screening (rapidly mobile population of pilgrims, the availability of imaging, sample collection, storage, and processing equipment, and the availability of accurate and rapid diagnostic tests for TB and for ruling out MDR-TB) have hindered any large-scale TB cohort studies of pilgrims. Thus no studies have proactively screened pilgrims or KSA residents for TB using the latest in TB diagnostics such as the Xpert MTB/RIF assay.^{42,43,18,44,45} The transmission dynamics of circulating drug-sensitive and drug-resistant *M. tuberculosis* strains and their phylogenetic relationships remain undefined. The actual baseline burden of active TB, MDR-TB, sub-clinical TB, and TB co-morbidity with other communicable and non-communicable diseases in pilgrims remains to be determined. The impact of the transmission of drug-sensitive and drug-resistant strains of *M. tuberculosis* by pilgrims to local resident KSA populations who interact with them during the pilgrimage (and vice versa) also requires definition.

8. Opportunities for conducting priority TB research

The Hajj pilgrimage presents unique opportunities to conduct priority research utilizing the formidable processes and structures that are in place for handling millions of pilgrims.¹¹ Prior to departure, all pilgrims need to satisfy the pre-travel vaccination requirements and apply for a visa. Pilgrims need to be linked with specific Hajj travel agents who coordinate and supervise pilgrim cohorts; these cohorts remain together during the entire Hajj period until return. The KSA provides free healthcare to all pilgrims during the Hajj, and a Hajj Command and Control Centre oversees all infectious diseases issues. Planning for Hajj is meticulous and coordinated.¹¹ This includes numerous healthcare centres across all pilgrimage routes, thousands of healthcare workers, numerous mobile teams, and referral hospitals with inpatient and critical care facilities. At all ports of entry to the KSA, public health officials are present to ensure compliance with the pilgrim health requirements. There are holding areas and clinical examination rooms specifically for health screening of pilgrims arriving at the Hajj terminal of King Abdulaziz International Airport in Jeddah. Using electronic data recording and surveillance systems, the public health teams at the ports of entry continuously report to the Command and Control Centre for Communicable Diseases at the Hajj.¹¹

Thus there are unique opportunities to conduct a range of cohort and cross-sectional TB studies involving pilgrims and susceptible KSA resident staff at points of pilgrim entry and healthcare. These should be done at all stages of the Hajj, from the pre-Hajj preparative stage to arrival in Jeddah, throughout all stages of the Hajj in Makkah, and upon the return of the pilgrims to their country of origin. Furthermore, new rapid diagnostic platforms that can screen for all common causes of respiratory tract infections (viral and bacterial, including TB) are being developed,^{43,18} and opportunities now arise to define the relative importance of each causal pathogen.

9. Defining burden, transmission risk, and the optimal treatment, prevention, and control measures at the annual Hajj pilgrimage

From a public health perspective, there is a need for a practical and well-defined strategy to minimize the risk of transmission of *M. tuberculosis* and other respiratory tract pathogens at the Hajj and Umrah pilgrimages. Thus aligning the research on TB to the generic issue of respiratory tract infections will provide information that will serve the greatest practical clinical need of infectious diseases healthcare at the Hajj. Large-scale properly designed and controlled studies on the prevention, diagnosis, epidemiology, and management of TB in the context of the generic issue of respiratory tract infections are required for the results to be applicable to the large heterogeneous population of pilgrims. The evaluation of the burden of active TB disease (including MDR-TB) and that of LTBI in pilgrims and resident KSA staff, will require several cross-sectional and longitudinal cohort studies to be performed pre-Hajj, during the Hajj, and after the end of the Hajj (summarized in Table 1). The results of these studies will allow the development of an accurate evidence base, which will help in the formulation of international recommendations by WHO collaborating centres for mass gathering events and in the drawing up of guidelines for the optimal surveillance, screening, transmission risk, treatment, prevention, and control measures for TB at mass gathering events.

There are currently no specific recommendations to proactively detect or prevent TB in pilgrims or KSA residents during the Hajj. Whilst current KSA Ministry of Health guidelines focus on the use of facemasks during the Hajj to prevent respiratory tract infections, adherence to these measures has been difficult to implement in practice. There is a need for education campaigns to make the pilgrims and the KSA public aware of TB, and to facilitate the diagnosis of symptomatic cases. There is a need for case controlled studies on the benefits of educational interventions involving simple hygiene and cough etiquette measures prior to departure and during the Hajj period in reducing the transmission of *M. tuberculosis* and other respiratory tract infections.

The screening of pilgrims from high TB burden countries before travel could allow the detection and treatment of active pulmonary TB cases and prevent the transmission of *M. tuberculosis* infection to other pilgrims and KSA residents and Hajj staff. Basic screening based on the ability to produce a sputum sample (irrespective of health status) for examination with the Xpert MTB/RIF assay will allow the detection of active or sub-clinical cases of pulmonary TB, and of MDR-TB by proxy.⁴³ Longitudinal cohort studies of pilgrims from both high and low TB endemic areas with testing for LTBI using interferon-gamma response assays before departure, during the Hajj, and at 3 months after return from the Hajj, will provide information on the risk of acquiring *M. tuberculosis* and the risk of reactivation of LTBI during Hajj. This will also assist in defining transmission dynamics and patterns of both drug-sensitive and drug-resistant strains of *M. tuberculosis* through the use of molecular typing methods and whole genome sequencing directly on patient sputum.^{43,18,44–47} Such studies will add to our understanding of *M. tuberculosis* epidemiology and transmission dynamics. Since the acquisition of *M. tuberculosis* infection during the pilgrimage may not manifest as clinically active TB and may result in LTBI, long-term follow-up studies of pilgrims and KSA resident staff are required. In low TB burden countries, the screening of pilgrims for LTBI before and after Hajj could identify those cases that may benefit from preventive therapy.

Non-communicable diseases are common causes of hospital admission during the Hajj,⁴⁸ and the opportunity to screen for TB co-morbidity in pilgrims admitted for any cause of ill health should be taken to identify sub-clinical or undiagnosed cases of TB.⁴² There is a need for proactive studies that screen for active TB

among ill non-hospitalized and hospitalized pilgrims who can produce a sputum sample to determine the prevalence of TB during Hajj. The data could be stratified by country of origin and comorbidity with communicable and non-communicable diseases. Since pilgrims are always on the move, the establishment of well-equipped mobile health clinics with up-to-date laboratory equipment, including molecular biology facilities, would be required for the rapid diagnosis and identification of all pathogens causing respiratory tract infections, including TB and MDR-TB.^{43,18,44} Establishing a central registry of information collected at the Hajj, including data on genetic profiling and the drug resistance of isolates, should be included as part of the agenda for improving TB screening and services at the Hajj.

10. Conclusions

Accurate data on the actual burden of TB and transmission risk associated with mass gatherings are scarce and unreliable due to the small numbers studied and methodological issues. Developing an accurate evidence base for optimal surveillance, screening, transmission risk, treatment, prevention, and control measures for TB at mass gathering events is an important priority and will go a long way towards achieving the WHO post-2015 End TB Strategy goals. The Hajj pilgrimage presents unique opportunities to conduct priority research utilizing the formidable processes and structures that are in place for handling millions of pilgrims.

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