Tuberculosis during the Hajj religious mass gathering: occurrence, prevention, and management

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

By:

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Abstract

Background

Tuberculosis (TB) is a global health issue with significant morbidity and mortality. The Hajj religious mass gathering represents many of the risk factors for TB transmission and the disease has been reported among hospitalised pilgrims during the event. However, little data is available on the true burden of TB in Hajj or the management of TB cases in hospitals at the event including healthcare worker's (HCWs) knowledge, attitude and practice (KAP) regarding TB. Accordingly, the thesis consists of three separate, but integrated studies, each with own objectives, literature review, methodology, result and discussion sections. Thesis studies are as follows:

1. Active PTB among hospitalised and non-hospitalised pilgrims during the Hajj mass gathering
2. Management of hospitalised Pulmonary Tuberculosis (PTB) patients during the Hajj mass gathering
3. TB knowledge, attitude and practice among HCWs during the Hajj mass gathering

Aim

The overall aim of this research project is to provide evidence-base for improvement of TB prevention, management and control during the Hajj mass gathering. The outcomes could be beneficial to other mass gatherings worldwide and will enrich knowledge in the new scientific discipline of “mass gatherings medicine”.

Method

The study was conducted in Makkah, Kingdom of Saudi Arabia (KSA), the location of the Hajj over 2 Hajj seasons (2016-2017). Structured questionnaires and forms were used to collect information related to the study population (non-hospitalised and hospitalized pilgrims with productive cough, TB cases admitted to hospitals during Hajj and Hajj healthcare workers). Information was also collected in relation to the management of TB cases in Hajj and the knowledge attitude and practice of healthcare workers delivering services during the event regarding TB and its management. Sputum samples were also collected from the hospitalised and non-hospitalised pilgrims and tested for TB using the Xpert MTB/RIF assay.

Results

1. ***Active PTB among hospitalised and non-hospitalised pilgrims during the Hajj mass gathering***

   For non-hospitalised pilgrims, out of the 1,510 pilgrims tested, 10 (0.66%) had undiagnosed active PTB. Underlying health conditions and cough in the household were independent risk factors for TB among this population. For hospitalised pilgrims, among the 304 patients investigated, 9 (2.9%) had active PTB and most (77.7%) of these were missed by the hospitals including multidrug-resistant TB cases. Previous TB treatment was an independent risk factor for TB among this population after adjusting for other variables

2. ***Management of hospitalized PTB patients during the Hajj mass gathering***

   The study also documented the management of 32 confirmed TB patients during Hajj and explored the compliance of healthcare providers with the KSA TB management guidelines in hospitals during the mass gathering. Out of a maximum score of 10 for the selected TB management themes, the guideline compliance score was highest for infection prevention and control and surveillance (9.6) and identifying TB suspects (7.2). The least scores were obtained for treating TB (5.0) and diagnosing TB (3.0).

3. ***TB knowledge, attitude and practice among HCWs during the Hajj mass gathering***

   Finally, the study conducted a KAP survey among 540 HCWs from 13 hospitals serving pilgrims in Hajj. In general, HCWs had average knowledge (mean knowledge score of 52%), above average attitude (mean attitude score of 73%) and good practice (mean practice score of 81%) regarding TB, based on the scoring system and cut-off points developed in the current study.

Conclusions

The results of the current study suggest that there are a number of key challenges in relation to TB at the Hajj. These include undiagnosed and missed TB cases at the event, inadequacy of current national and international TB management guidelines in the context of Hajj and important knowledge gaps, negative attitudes and wrong practices among HCWs in relation to TB. As such, TB during the Hajj mass gathering needs more attention from the scientific community and Hajj stakeholders. A raft of recommendations are proposed to optimize awareness, screening, management and treatment, prevention, and control measures for TB during Hajj as well as other mass gatherings both within Saudi Arabia and worldwide.

Declaration

I certify that I am responsible for the submission of this thesis and hereby confirm that it is my original work unless referenced or specified in the acknowledgements and footnotes. The original work presented in this thesis has not been submitted to this or any other related institution for any award or degree.

Dedication

This research is dedicated to my mother, Al Subaie Rafiah my role model in life. I pray that Allah give her good health to support me in my future career and guide me as she does always. I also dedicated this research to my husband, my best friend, my mentor and my pillar of strength, Prof. Khalid bin Mohammed Alaiban, who believes in me, continuously providing support and encouragement during my difficult times, and for being with me in this journey.

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Abbreviations

Abbreviations	Definition
ACSM	Advocacy, Communication and Social Mobilization
AFB	Acid-Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
AMK	Amikacin
aOR	Adjusted Odd Ratio
ART	Antiretroviral Therapy
ARTI	Annual Risk of Tuberculosis Infection
BCG	Bacillus Calmette-Guérin
BICSL	Basic Infection Control Skills License
CAP	Capreomycin
CAT II	Category 2
CBC	Complete Blood Count
CDC	Centres for Disease Control and Prevention
CI	Confidence Interval
CIP	Ciprofloxacin

Abbreviations	Definition
COPD	Chronic Obstructive Pulmonary Disease
CrI	Credible Interval
DOT	Directly Observed Treatment
DOTS	Directly Observed Therapy Short Course
DST	Drug-sensitivity Testing
EMB	Ethambutol
ER	Emergency Room
FDC	Fixed-dose Combination
Freq	Frequency
GCP	Good Clinical Practice
HCW	Healthcare Worker
HEPA	High Efficiency Particulate Air
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases

Abbreviations

Abbreviations	Definition
ICU	Intensive Care Unit
IGRA	Interferon-Gamma Release Assay
INH	Isoniazid
IPC	Infection Prevention and Control
IQR	Inter Quartile Range
IRIS	Immune Reconstitution Inflammatory Syndrome
IRR	Incidence Rate Ratio
KAN	Kanamycin
KAP	Knowledge, Attitude and Practice
KSA	Kingdom of Saudi Arabia
LED	Light-Emitting Diode
LEV	Flevofloxacin
LPA	Line Probe Assay
LTBI	Latent Tuberculosis Infection
MDR	MultiDrug-Resistant
MDR-TB	Multi-Drug Resistant Tuberculosis
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MOH	Ministry of Health
NIOSH	National Institute for Occupational Safety and Health
NTP	National TB Control Program
O&G	Obstetrics and Gynaecology
OR	Odd Ratio
PPE	Personal Protective Equipment
PTB	Pulmonary Tuberculosis
PZA	Pyrazinamide
QFT	Quantiferon
QFT-GIT	Quantiferon-TB Gold In Tube
RIF	Rifampicin

Abbreviations

Abbreviations	Definition
RR-TB	Rifampicin-Resistant Tuberculosis
SARS	Severe Acute Respiratory Syndrome
SAT	Self-Administered Treatment
SD	Standard Deviation
SDGs	Sustainable Development Goals
STM	Streptomycin
TB	Tuberculosis
TST	Tuberculin Skin Test
UK	United Kingdom
UN	United Nations
USA	United States of America
UVGI	Ultraviolet Germicidal Irradiation
VOT	Video-Observed Treatment
WHO	World Health Organization
XDR	Extensively Drug-Resistant
XDR-TB	Extensively Drug-Resistant Tuberculosis

AIM, OBJECTIVES AND THESIS ROADMAP

Thesis roadmap

Mass gatherings introduce a number of public health threats to the host country/community. In their simplest definition, mass gatherings involve large numbers of people gathering in a particular place for a specific period of time. Hence, one of the major public health threats at mass gatherings are infectious diseases. Mass gatherings can increase the risk of an already present communicable disease or introduce a completely new infectious disease threat to the host (World Health Organization, 2008b). Mass gatherings with international dimensions are concerning as these events are capable of importing, spreading and exporting infectious agents worldwide in a relatively short time as evidenced by the international meningococcal disease outbreaks associated with the Hajj (Yezli et al., 2016).

Tuberculosis is a global health issues with significant mortality and morbidity. The WHO aims to end the global TB epidemic, with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB (World Health Organization, 2015a). Early detection and appropriate management of TB cases as well as prevention of the disease are cornerstones of this strategy. Mass gatherings, such as the Hajj, are potentially an underappreciated source for TB transmission and could undermine the WHO's ambitious targets. The Hajj represents many of the risk factors for TB transmission and reactivation of LTBI. It is attended by millions of pilgrims, many from TB-endemic countries, with a substantial proportion being elderly with underlying health conditions. Crowded conditions, physically demanding religious rites well as other factors render pilgrims susceptible to infections and facilitate transmission of respiratory agents including TB. Hence, attending the event was reported to be a risk for TB infection (Wilder-Smith et al., 2005).

On the other hand, Hajj, and other mass gatherings, could be a missed opportunity for global control of TB by identifying undiagnosed cases, early detection of cases, as well as preventing spread among attendees and the international community. For this to occur, it is important to study TB at the Hajj and identify potential issues in the management and control of the diseases that could contribute to the spread of the disease or poor outcome for cases.

Tackling these issues with evidence-based policies that are effective and practical would improve patients' outcome and the prevention, control and management of the disease at the Hajj as well as other mass gatherings worldwide. Therefore, contributing to the WHO's End-TB targets.

TB at Hajj is multifaceted, complex topic and improving prevention, control and management of the disease at this event requires identification of key knowledge gaps in the field, a better understanding of the current status and practices related to TB in Hajj, identifying issues and areas of concerns and recommending and implementing evidence-based strategies to address these issues. The current work aims to contribute to the above by investigating certain aspects of TB at the Hajj that would together add to the limited knowledge on the topic as well as identify key areas for improvement in the detection, management and prevention of the disease at the mass gathering. These areas that could contribute to the transmission of TB during and after the Hajj include missed or undiagnosed active cases and the mismanagement of TB confirmed cases which may be a result of lack of appropriate guidelines or poor knowledge or practice among HCWs involved. Accordingly, the current work will investigate the following four topics:

1. Active PTB among non-hospitalised pilgrims during the Hajj mass gathering
2. Active PTB among hospitalised pilgrims during the Hajj mass gathering
3. Management of hospitalized PTB patients during the Hajj mass gathering
4. TB knowledge, attitude and practice among HCWs during the Hajj mass gathering

General aim and objectives

General aim

The overall aim of this research project is to provide evidence-base for improvement of TB prevention, management and control during the Hajj mass gathering. The outcomes could be beneficial to other mass gatherings worldwide and will enrich knowledge in the new scientific discipline of "mass gatherings medicine". As such, the current work has the below specific objectives of the three main studies in the thesis and will follow the roadmap highlighted in Figure 1.

Specific objectives

The thesis has below specific objectives that are addressed through the following studies

A. *Active PTB among hospitalised and non-hospitalised pilgrims during the Hajj mass gathering*

1. To determine the occurrence of active pulmonary TB (both sensitive and drug resistant) among non-hospitalized pilgrims with cough from medium and high burden TB countries regardless of health status.
2. To determine the occurrence of active pulmonary TB (both sensitive and drug resistant) among hospitalised pilgrims with cough during Hajj, regardless of the admission diagnosis.

B. *Management of hospitalized PTB patients during the Hajj mass gathering*

A. To document how TB patients are managed during the Hajj pilgrimage and whether this follows current guidelines.

C. *TB knowledge, attitude and practice among HCWs during the Hajj mass gathering*

1. To determine HCWs' knowledge and knowledge gaps regarding TB and its management and attitudes and behaviours among HCWs that could facilitate TB transmission or impact TB management.

Active pulmonary tuberculosis among non-hospitalised pilgrims during the Hajj mass gathering

Undiagnosed TB cases in the community have been reported in numerous studies (Deribew et al., 2012, Hoa et al., 2010, Kapata et al., 2016, Onozaki et al., 2015, Senkoro et al., 2016, Wood et al., 2007, Zaman et al., 2006, Zaman et al., 2012,). Such cases are an important risk for TB spread and ongoing community transmission and represent a challenge for TB control efforts worldwide. Only one study reported active PTB among non-hospitalised pilgrims in Hajj (Yezli et al., 2017b). The study was a proof of concept and limited in its study population as it did not include pilgrims from countries with some of the largest Hajj pilgrim populations and those with high MDR-TB rates. The current work will identify the burden of undiagnosed TB (both sensitive and MDR) among non-hospitalised pilgrims. The work will attempt to confirm the results of the previous study and highlight that active PTB among non-hospitalised pilgrims occurs in Hajj and that the latter is a significant risk for public health at the event and for global health security. It will also investigate pilgrims from a larger number of countries, those with high Hajj pilgrims' populations and those with high MDR-TB rates.

If undiagnosed active MDR-TB is detected in Hajj, this would be an ever bigger threat that needs addressing. Proof of undiagnosed active TB among non-hospitalised pilgrims would necessitate a number of public health interventions which may include screening pilgrims for the diseases pre-event. Logistically, among other limitations, it would be very difficult to screen all pilgrims for TB before Hajj. Hence, identifying at-risk populations that could undergo targeted screening would make the process more efficient, feasible and less costly. As such, the current study will also investigate factors associated with undiagnosed TB among non-hospitalised Hajj pilgrims. This will allow the identification of potential risk groups that could be targeted for appropriate interventions or investigated further in future research.

Active pulmonary tuberculosis among hospitalised pilgrims during the Hajj mass gathering

TB has been reported among patients during Hajj (Al-Orainey, 2013, Alzeer et al., 1998, Madani et al., 2006). Studies have reported that a significant proportion of TB cases are missed among patients admitted to hospitals worldwide (Balabanova et al., 2011, Bobrowitz, 1982, Juul, 1977, Katz et al., 1985, Lee and Ng, 1990, Makela et al., 1971, Roberts et al., 1971, Rosenthal et al., 1975). A number of reasons can lead to failure to diagnosed TB among patient including lack of or limited symptoms, not testing for TB when people do present to health facilities and diagnostic tests that are not sufficiently sensitive or specific to ensure accurate identification of all cases. Failure to diagnose and adequately treat TB among hospitalised patients could lead to premature death and unrecognized transmission of *M. tuberculosis* (Casey, 1966, 1968, Johnson and Johnson, 1959, Medrano et al., 2014, Rosenthal et al., 1975, von Delft et al., 2015, Whittington, 1983). This puts family members, other patients and the community at increased risk of TB infection and subsequent disease. In addition, the complex contact patterns between HCWs and patients potentiate the spread of TB disease in the healthcare setting, resulting in an increased occupational risk of TB infection and disease among HCWs, practicing medical students and patients (Alele et al., 2018, Boudreau et al., 1997, Sepkowitz, 1994). The latter are an already vulnerable population more susceptible to infection and worsening outcomes. Undiagnosed MDR-TB in healthcare setting has also been reported and it represents an even bigger threat given that it is harder to treat with higher mortality rate (Bates et al., 2012, Bates et al., 2015, Onozaki et al., 2015).

Missed or undiagnosed TB among patient at mass gatherings has more serious consequences as it has the potential to transmit infection to a larger number of people given that healthcare facilities are usually busier or working to surge capacity during these events as well as the crowded conditions outside these facilities. The above is applicable to Hajj where missed TB cases among patients in busy hospitals with quick patients' turnaround represent a serious threat to patients, Hajj pilgrims, HCWs, the local population and the international community at large. No study investigated undiagnosed or missed TB cases during Hajj. Hence, the current work will attempt to define the burden of missed TB cases among hospitalised pilgrims during the event. This by identifying undiagnosed TB among patients admitted to hospitals during Hajj regardless of their admission diagnosis. This work will also investigate factors associated with missed TB among patients so that at-risk populations can be determined and more attention can be given to these populations during patient management in Hajj. This may include considering these populations as suspect TB cases and investigated for the disease on admission to hospitals. The study will also identify specific factors that could contribute to missed TB cases in hospitals and further transmission such as lack of appropriate testing techniques, mismanagement of patients on admission and substandard infection prevention and control practices. These could also be addressed to reduce the risk of undiagnosed TB among patients and transmission in hospitals.

Management of hospitalized pulmonary tuberculosis patients during the Hajj mass gathering

Appropriate management of TB cases is key in the prevention and control of TB. Early detection of cases and their management with fitting treatment regimen and infection prevention practices improve patient outcome and reduce the risk of transmission of the disease and development of antibiotic resistance (World Health Organization, 2011a, 2017a,). Although there are Saudi and international TB guidelines on the management of TB, currently there are no specific guidelines on the management of the disease at mass gatherings including Hajj. The TB management approaches during Hajj remained largely undocumented, and it is unknown whether these are consistent with the KSA and international TB management guidelines (World Health Organization, 2011a, 2017a, Saudi Ministry of Health, 2014). Hence, this work will also attempt to document the management of TB patients during Hajj and explored the compliance of healthcare providers with the KSA TB management guidelines in the Saudi MOH hospitals during the mass gathering.

Compliance will be evaluated against four selected TB management themes: identifying TB suspects, diagnosing TB cases, treatment of TB cases and finally, infection prevention and control and surveillance.By documenting the management of confirmed TB cases during Hajj from the moment they present to the hospitals until the cases are resolved, compliance with TB management standards can be evaluated through this work. In addition, various aspects of TB management during Hajj can be documented and key gaps/malpractices in the TB patients' journey in the hospital can be identified for improvement and interventions. This work will also report on the characteristics of the confirmed TB cases admitted to hospitals during Hajj which may help identify at-risk populations that should be investigated for TB for the early detection, diagnosis and treatment of TB. Outcomes from this work can contribute to the national and international guidelines for TB management by providing key information regarding management at mass gatherings specifically, which may differ from the standard guidelines in non-events settings.

Tuberculosis knowledge, attitude and practice among healthcare workers during the Hajj mass gathering

The early diagnosis and appropriate management of TB cases by a knowledgeable and skilled healthcare workforce are integral for the success of TB control strategies. HCWs are key component of the success of any TB program, yet they are also at increased risk of TB infection and disease. High level of knowledge, good attitude and correct practice among HCWs in relation to TB are important factors in the appropriate management of TB cases and reducing the risk of transmission of the disease including in the healthcare setting and to HCWs themselves (World Health Organization, 2008a). Knowledge deficit regarding TB among HCWs may result in substandard care, ineffective service provision, inefficient resource use, and further inequities in health outcomes as well as risk of TB transmission and development of resistance (Langendam et al., 2012, Marahatta, 2010). In addition, the knowledge and attitude of HCWs towards TB will determine the type and quality of information passed on to the patients during health education (Isara and Akpodiete, 2015). As such, the knowledge, attitude and practices of health professionals related to TB affect not only themselves and their individual patients, but also the community at large.

This work will evaluate the knowledge, attitude and practice of HCWs deployed during Hajj regarding TB and its control. It will also identify factors associated with good/poor KAP including those related to the type of HCWs, length of experience, experience treating TB patients as well as education level and specific training regarding TB. The outcomes of these investigations will determine HCWs' knowledge and knowledge gaps regarding TB and its management and attitudes and behaviours among HCWs that could facilitate TB transmission or impact TB management during Hajj. In addition to providing evidence base for appropriate strategies to improved HCWs KAP regarding TB and its management, this work will also identify specific HCWs populations that may need to be targeted with tailored interventions such as enhanced training and education.

Thesis structure

While this work will investigate different aspects of TB management and control at the Hajj, many of these are interconnected in the larger context of preventing TB at mass gatherings. This work will lead to a better understanding of TB at the Hajj, identifying important areas of improvement and investments as well as providing a number of practical recommendations. Put all together, this work will contribute to developing evidence-based policies to optimize awareness, surveillance, screening, management and treatment, prevention, and control measures for TB at Hajj and other mass gatherings worldwide. Accordingly, the thesis is structured chapters that reflects the above and based on study objectives. Each study has its own literature review, methodology, result and discussion sections. Thesis chapters are as follow:

Chapter 1: Tuberculosis and the Hajj mass gathering

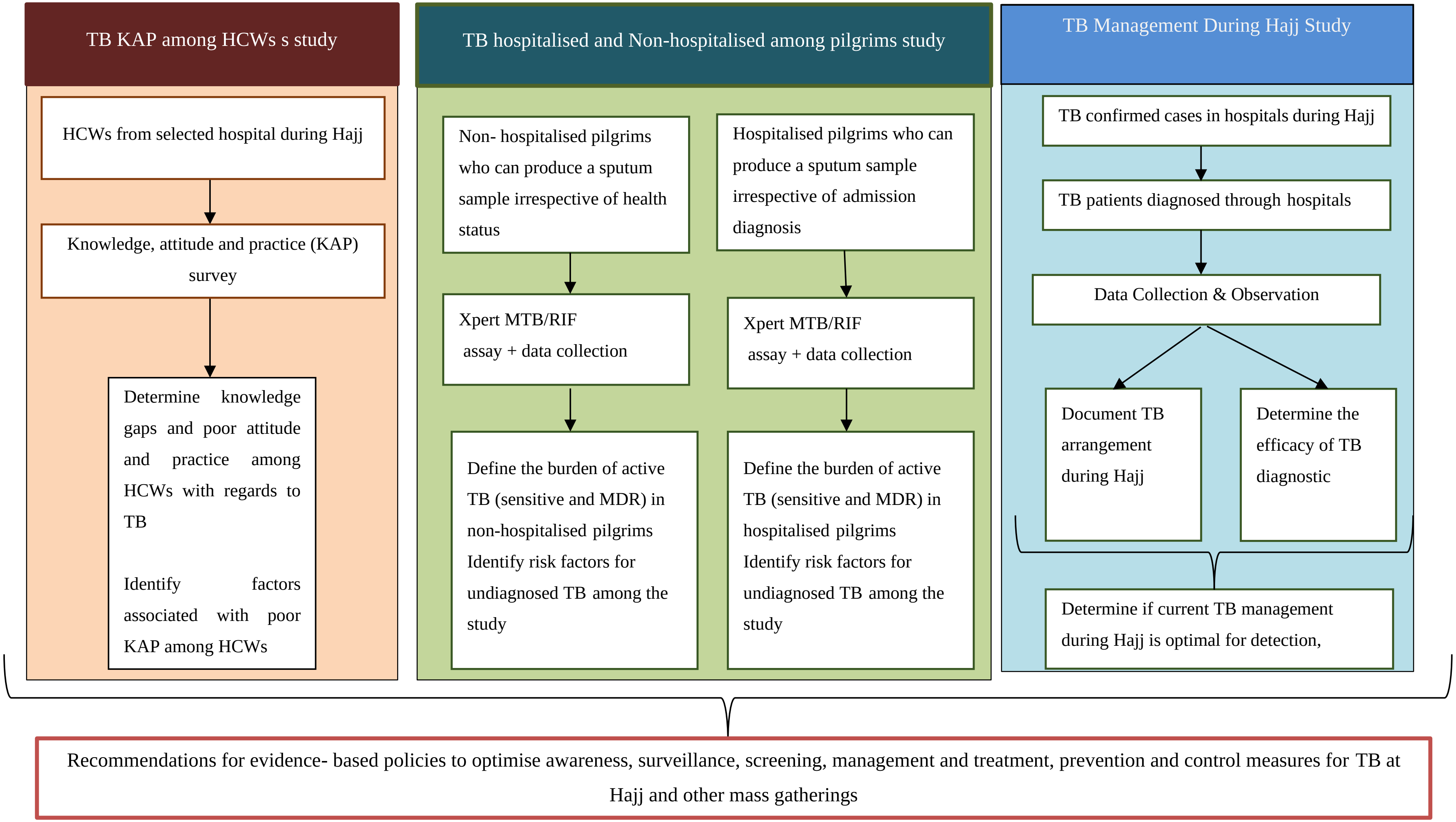
Chapter 2: Active pulmonary tuberculosis among hospitalised and non-hospitalised pilgrims during the Hajj mass gathering

Chapter 3: Management of hospitalized pulmonary tuberculosis patients during the Hajj mass gathering

Chapter 4: Tuberculosis knowledge, attitude and practice among healthcare workers during the Hajj mass gathering

Chapter 5: Summary and recommendations

Figure 1. Thesis roadmap and methodology for the three studies



Chapter 1: Tuberculosis and the Hajj mass gathering

1.1 Mass Gatherings

While the term “Mass Gathering” is increasingly used in academic literature, there is actually no international consensus on the definition of the term. Traditionally, a mass gathering event was defined as a group of over a 1,000 people assembled at a particular location for a specific purpose and for a defined period of time. Nevertheless, most of the published literature report larger events accounting for more than 25,000 participants (Locoh-Donou et al., 2013, World Health Organization, 2008b). This definition is however limiting as it only considers the size of the crowd, which is but one descriptor of a varied gathering of human beings at a mass gathering event (De Lorenzo, 1997, Locoh-Donou et al., 2013).

Some authors defined mass gatherings from a health prospective, considering a mass gathering event as a situation during which a large gathering of people occurs and results in limited access to patients, causing delayed public safety response to medical emergencies (Arbon, 2007, Locoh-Donou et al., 2013). While going beyond the size of the crowd, this definition is also restricting the term to a specific aspect of health related to delivery of medical care. The World Health Organization (WHO) definition also takes a broader view of mass gatherings to include the public health dimensions and defines mass gatherings as events attended by a sufficient number of people to potentially strain the public health resources of the community, city, or nation hosting the event (World Health Organization, 2008b).

The WHO definition is purposefully not linked to the size of the gathering or the number of people involved because each community has a different capacity to manage crowds of people, with some systems, for example, airports or market places, managing upwards of 100,000 people on a daily basis with minimal difficulties (World Health Organization, 2015d). Mass gatherings differ in many aspects including the characteristics of the crowds involved, the location of the event, the type of the event, and the public health risks involved. Mass gatherings can be either planned or spontaneous and recurrent or sporadic (World Health Organization, 2015d).

Planned mass gatherings are scheduled in advance, and may include sporting, social, cultural, religious, and political events. Examples include: music festivals, Olympic and Paralympic Games, the Super Bowl, the World Cup, pilgrimages such as the Hajj and the Kumbh Mela and political rallies and protest (World Health Organization, 2015d, Yezli and Alotaibi, 2016). Spontaneous mass gatherings by their nature are more difficult to plan for and may include events, such as funerals of religious and political figure (World Health Organization, 2008b, 2015d). In addition, some also consider the gatherings of displaced populations due to natural disasters, conflicts, and wars as mass gatherings (World Health Organization, 2015d). Mass gatherings can pose several significant public health challenges to the host and the global community. This is particularly true for mass gatherings with international dimensions. For instance, mass gatherings can place a significant stress on the health system of the host country and require intersectoral approaches to risk mitigation and coordination across multiple disciplines, sectors, and ministries (World Health Organization, 2015d). Mass gatherings can also introduce infectious and non-infectious public health threats to the local, national, or international populations during or after the events. International outbreaks of infectious diseases after mass gatherings such as meningococcal disease related to the Hajj and to the World Scout Jamboree are examples of such threats (Smith-Palmer et al., 2016, Yezli et al., 2016). In addition to the above, mass gatherings can introduce the risk of deliberate action against these events, increasing the likelihood of emergencies resulting in a significant number of casualties (World Health Organization, 2015d).

1.2 The Hajj mass gathering

According to Islam, every physically and financially able Muslim must undertake the Hajj, pilgrimage to the Kingdom of Saudi Arabia (KSA), once in his lifetime. During Hajj, millions of Muslims retrace the footsteps of the Prophet Mohammed, undertaking identical rituals (Ahmed et al., 2006). Hajj represents the culmination of years of spiritual preparation and planning. Once they have completed the pilgrimage, pilgrims are given the honorific title Hajji (pilgrim) (Gatrad and Sheikh, 2005). The Hajj is one of the largest and most geographically, ethnically, and culturally diverse annual mass gatherings in the world, attended by more than 2 million pilgrims from over 180 different countries each year (Yezli et al., 2017a). The number of pilgrims attending Hajj has been gradually increasing over the years to reach around 3 million pilgrims in 2012 compared with only 135,265 in 1954 (Alotaibi et al., 2017).

There was a reduction in the number of pilgrims attending Hajj in the last few years as limited permits were granted due to construction work to expand the Sacred Mosque (Yezli et al., 2017a). Once the expansion work will finish, the number of pilgrims attending Hajj is expected to more than double in the coming few years.

The Hajj rituals officially start on the 8th day of the 12th month of the lunar Islamic calendar called "Dhul-Hijjah", but most pilgrims arrive to Makkah few days or weeks earlier. As the lunar calendar lags behind the solar calendar by approximately 10 days every Gregorian year, Hajj falls in different parts of the Gregorian calendar each year. The Hajj journey is highlighted in Figure 2. On arrival at Makkah, each pilgrim, makes seven circumambulations (Tawaf) around the Ka'aba (the building Muslims consider the house of God). On the 9th of the month of "Dhul-Hijjah", pilgrims leave for the Plain of Arafat, around 20 Km east of central Makkah, where the Hajj culminates in the "Day of Standing". From noon until sundown, dressed in the simplest possible garb made up of two pieces of unstitched cloth for men (Ihram), with women wearing their usual clothing with a headscarf, pilgrims spend much of the day standing in humility and prayer at the Mount Arafat(Ahmed et al., 2006, Gatrad and Sheikh, 2005). On the way to Arafat, pilgrims make overnight stop in Mina (around 5 Km to the east of central Makkah), and in Muzdaliffah (around 10 Km from central Makkah) on return. On returning to Mina, the pilgrim stops alJamarat to stone the pillars that are effigies of Satan. The new Hajjis then make animal sacrifices (usually by proxy) as thanks for accepted Hajj. After a farewell *Tawaf*, the pilgrims leave Makkah(Ahmed et al., 2006, Gatrad and Sheikh, 2005). While the Hajj rituals take place in Makkah, many pilgrims also travel to the holy city of Medina, north of Makkah, where the Prophet Mohammed is buried (Yezli et al., 2017a).

1.3 Health risks at the Hajj

As a major international mass gathering Hajj is associated with number of public health risks that may affect the participating pilgrims, the workers involved in the running, management and delivery of service during the event, the local population as well as the international community. As such, KSA directs huge investments each year towards the optimum planning and management of Hajj and preventing, minimizing and responding to public health emergencies (Ahmed et al., 2006, Ahmed Q.A. et al., 2009, Alotaibi et al., 2017, Memish, 2013, Memish and Al-Rabeeah, 2013).

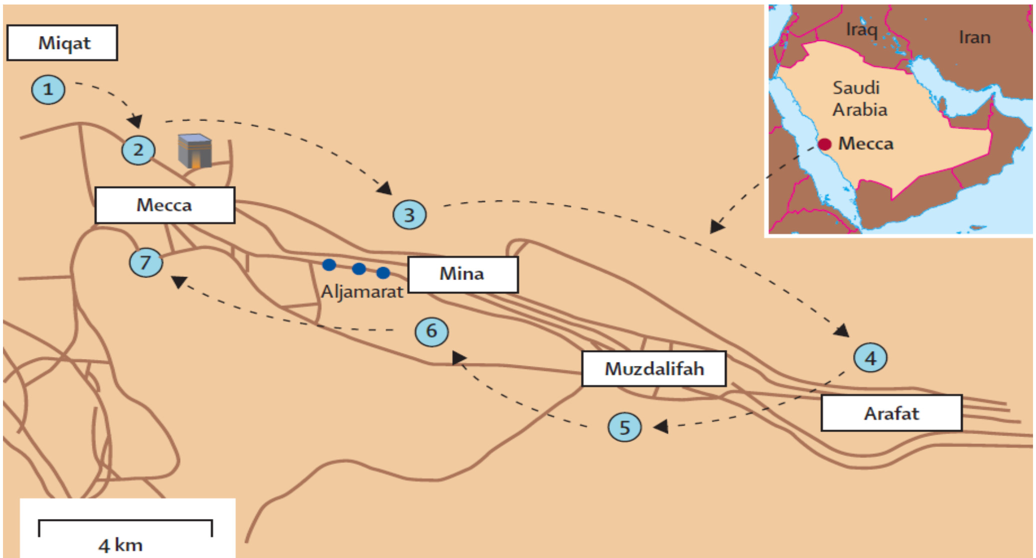
Given the characteristics of the Hajj population and the international dimension of the event, communicable diseases are one of the major public health threats in Hajj and for global health security. In Hajj unhygienic practices and close contacts between pilgrims in overcrowded situations during the rituals, as well as international travel, increase the risks of outbreaks and the spread of infectious diseases among pilgrims and other individual (Alotaibi et al., 2017).

The threat of transmission of respiratory pathogens are particularly relevant for the event including tuberculosis (TB), influenza and more recently the Middle East Respiratory Syndrome coronavirus (MERS-CoV). The event has been linked to the importation and globalization of respiratory pathogens (Memish et al., 2015a). Historically, several outbreaks of infectious diseases have been reported at the Hajj. These include an outbreak of cholera during the 1865 Hajj that caused an estimated 30,000 deaths among pilgrims and a number of international Hajj-related outbreaks of meningococcal diseases in 1987, 2000 and 2001(Alotaibi et al., 2017, Yezli et al., 2016). Also, in recent years, Hajj took place during outbreaks of number of emerging infectious diseases and diseases declared by the WHO as "Public Health Emergency of International Concern". These include, viral haemorrhagic fever syndromes such as those caused by Rift Valley fever virus, Alkhurma virus and Ebola virus, respiratory diseases such as Severe Acute Respiratory Syndrome (SARS) and MERS, Avian influenza (H5N1), and Swine influenza A (H1N1), and Zika (Ahmed et al., 2006, Bennett and Carney, 2017). Thankfully, due to pragmatic public health preparedness strategies for Hajj, no major Haj-related outbreaks of such diseases have been reported. Other communicable diseases threats of importance during Hajj include traveller's diarrhoea (Ahmed et al., 2006). Outbreaks of cholera have been reported in Hajj as well as cases of food poisoning. Skin infections and Blood-borne diseases are also of concern (Ahmed et al., 2006, Gatrad and Sheikh, 2001). The threat of the latter is exacerbated by the practice of unhygienic shaving of the heads, which is part of the rituals to complete Hajj for Muslim men. Such practices can increase the risk of transmission of blood-borne disease, including hepatitis B and C, and HIV (Gatrad and Sheikh, 2001). The KSA authorities have introduced a number of strict regulations to eliminate these practices including legislative stance to prevent unlicensed barbers from operating during the Hajj, testing of barbers for hepatitis B and C , and HIV, and the use of disposable single-use blades (Al-Salama and El-Bushra, 1998).

While communicable diseases such as respiratory tract infections are the major cause of morbidity and hospital admissions during Hajj, non-communicable diseases are the main cause of mortality during the event (Ahmed et al., 2006, Al-Ghamdi et al., 2003). Given the characteristics of the pilgrims' population (roughly 25% are at least 65 years old) (Ebrahim et al., 2009).

An important proportion of Hajj pilgrims come to the event with underlying health conditions (AlBarrak et al., 2018, Alzeer et al., 1998, Gautret et al., 2015, Khan et al., 2006, Madani et al., 2006, Mandourah et al., 2012, Memish et al., 2014, Shirah et al., 2017, Yezli et al., 2017b). Performing the religious rites under various stressors can exacerbate these conditions. It has been reported that cardiovascular disease is the most common cause (43%) of death during the Hajj (Ahmed et al., 2006). Heat-related illnesses, especially, heat exhaustion and heatstroke are a leading cause of morbidity and mortality during the Hajj, particularly in summer. For example, in August 1985, among the 852,000 pilgrims more than 2,134 were victims of heatstroke, of whom 1,000 died in just few days (Ghaznawi and Khalil, 1988). There were also 15,560 pilgrims that suffered from heat exhaustion. While major interventions to reduce heat-related illnesses over the year have reduced the incidence of such conditions, extreme heat remains a major public health concern during Hajj (Abdelmoety et al., 2018, Aleeban and Mackey, 2016). Other health risks at Hajj include fire-related injuries, risks of deliberate acts against the event and risk of trauma such as that related to stampedes and crushes as evidenced by the recent 2015 Hajj crush (Ahmed et al., 2006, Khan and Noji, 2016).

Figure 2. The Hajj journey*



*From Ahmed et al.(Ahmed et al., 2006)

1.4 Tuberculosis

Tuberculosis (TB) is an infectious disease usually caused by the "slow-growing, chemo-organotrophic, non-motile, non-spore-forming, aerobicbacillu bacteria *Mycobacterium tuberculosis*" (Gordon and Parish, 2018). TB may infect any part of the body, but most commonly occurs in the lungs, known as pulmonary tuberculosis (PTB) (Lyon and Rossman, 2017).

Extra-pulmonary TB occurs when TB develops outside of the lungs, although the latter may coexist with PTB. Extra-pulmonary sites of infection commonly include lymph nodes, pleura, and osteoarticular areas, although any organ can be involved (Golden and Vikram, 2005). General signs and symptoms of TB include fever, chills, night sweats, loss of appetite, weight loss, and fatigue (Lyon and Rossman, 2017).

TB remains a global public health problem with significant morbidity and mortality. In 2017, the WHO estimated that 10 million people (range, 9.0–11.1 million) developed TB, 9% of whom were infected with the human immunodeficiency virus (HIV) (World Health Organization, 2018b). Two thirds of these were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). These and 22other countries in the WHO's list of 30 high TB burden countries accounted for 87% of the world's cases. Worldwide in 2017, an estimated 558,000 people (range, 483,000–639,000) developed TB that was resistant to rifampicin (RR-TB), 82% of whom had multidrug-resistant TB (MDR-TB). Three countries accounted for almost half of the world's cases of MDR/RR-TB: India (24%), China (13%) and the Russian Federation (10%). Extensively drug resistant TB (XDR-TB) accounted for about 8.5% of the MDR-TB cases (World Health Organization, 2018b). Also, in 2017, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people and there were an additional 300,000 deaths from TB (range,266,000–335,000) among HIV-positive people (World Health Organization, 2018b). This makes TB one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (above HIV/AIDS).

Latent tuberculosis infection (LTBI), defined as " a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinical and radiological disease'' (Mack et al., 2009), is also important in TB epidemiology. Based on information available on the frequency of positive tuberculin skin test (TST) response, it is estimated that one third of the world's population is infected with *M. tuberculosis* (Dye et al., 1999). The vast majority of infected persons have no signs or symptoms of TB disease and are not infectious, but they are at risk for developing active TB disease and becoming infectious. Approximately 5%-10% of those infected will develop active disease, and most will be capable of infecting others (Comstock et al., 1974, Jensen et al., 2005). Hence, individuals with LTBI represent an important source of new cases of active TB.

1.5 Tuberculosis in Saud Arabia

Saudi Arabia is not considered by the WHO as a high TB burden country. However, despite the remarkable economic and social developments and the large investments in health care services over the past 30 years, TB control still faces challenges in the Kingdom (Al-Orainey et al., 2013). In 2017, in a population of around 33 million, the WHO reported a TB incidence rate of 10/100,000 in Saudi Arabia. The total cases of TB notified to the WHO in 2017 from the Kingdom were 2,925 (www.who.int/tb/data). KSA is a fast-developing country that has experienced great changes over the previous decades. By improving its standard of living and improving social and health services, KSA has succeeded in minimizing infectious disease-related mortalities. With this rapid development, the Kingdom has become a major destination for many immigrants who currently make up about one-third of the Saudi population (Almutairi et al., 2018). Most of these originate from developing countries many of which are TB high burden countries such as India, Pakistan, Bangladesh and Indonesia. In addition to its resident population, Saudi Arabia hosts the Hajj and Umrah where each year an estimated 10 million pilgrims from over 180 countries travel to the Kingdom to attend these mass gatherings (Yezli et al., 2017a). These pilgrims, mostly elderly, many from poor countries where TB is endemic, gather in close contact to perform physically demanding religious rites. In such conditions, the potential for TB transmission is expected to be high (Al-Orainey, 2013). These factors influence TB epidemiology in the KSA and beyond and make the country particularly prone to the importation and exportation of TB and present many challenges to KSA in controlling TB (Al-Orainey et al., 2013, Almutairi et al., 2018).

Saudi health authorities implemented an NTP for over 30 years (Abouzeid et al., 2012, Al-Orainey et al., 2013). Due to the social stigma accompanying TB in KSA, TB care is incorporated into the general health services. It is mainly based on finding and treating active TB patients, improving methods of reporting and laboratory services. Diagnosis of TB is based mainly on sputum smear microscopy, radiography, mycobacterial culture, histopathology, in addition to molecular techniques available in some referral laboratories (Abouzeid et al., 2012). Bacillus Calmette-Guérin (BCG) vaccination is mandatory to all children at birth, and TB treatment is offered freely to all patients in government hospitals (Al-Orainey et al., 2013). In the year 2000, the NTP started to implement DOTS in all regions of the Kingdom. This was accompanied by a policy change regarding to healthcare for non-Saudis. Before 2000, non-Saudis were not allowed to reside permanently in the Kingdom. They were not allowed access to free government healthcare facilities, and they did not access private healthcare facilities for fear of deportation (Abouzeid et al., 2012). Hence, many non-Saudi TB patients were not diagnosed or registered, leading to under reporting. Since the end of 2000, non-Saudi patients with symptoms suggestive of TB were allowed to access governmental healthcare facilities free of charge and were allowed to remain in the Kingdom (Abouzeid et al., 2012, Almutairi et al., 2018). This policy change encouraged non-Saudis to use government health care facilities, thus increasing case detection rates in non-Saudis. However, this did not eliminate the possibility to be dismissed by their employer for having TB, which might still prevent some from seeking diagnosis and treatment (Almutairi et al., 2018).

Al-Orainey and colleagues (Al-Orainey et al., 2013) reported on the incidence trends of TB in Saudi Arabia over a 20-year period from 1991 to 2010. A total of 64,345 TB cases were reported to the Ministry of Health during the study period. Of these, there were 46,827 (73%) PTB cases and 17,518 (27%) extra-PTB. The annual incidence of TB ranged between 14 and 17/100,000 over the study period. The majority of TB cases (62%) were males. TB incidents rates among males in KSA have generally been higher than that of females especially among Saudi nationals (Abouzeid et al., 2012, Almutairi et al., 2018). This observation has been linked to the fact that until recently, males in KSA were more engaged in public events than females and to the stigma of being diagnosed with TB among Saudi females (Abouzeid et al., 2012, Almutairi et al., 2018).

Out of the 64,345 TB cases in KSA between 1991 and 2010, 33,468 (52%) were Saudi patients and 30,837 (48%) were non-Saudis (Al-Orainey et al., 2013). Saudis had an incidence between 8.6 and 12.2/100,000 while non-Saudis had an incidence of 24.3-32.3/100,000. TB incidence showed a significant rising trend over the first 10 years of the study period. The trend for non-Saudis then started to significantly decline, while the trend for Saudis remained flat over the last 10 years (Figure3) (Al-Orainey et al., 2013). In general, numerous studies have reported that the foreign population in Saudi Arabia have 2-3 times higher TB incidence than Saudi nationals (Abouzeid et al., 2012, Al-Orainey et al., 2013, Almutairi et al., 2018, Gleason et al., 2012). The most represented countries are Indonesia, Yemen, India, Pakistan, Bangladesh and the Philippines (Abouzeid et al., 2012, Almutairi et al., 2018). The observation that non-Saudis have higher incidence of TB has been attributed to a number of factors including the fact that most of the immigrants in KSA come from countries with high TB incidence rates such as Pakistan, India, Bangladesh and Indonesia and not all of them are screened for TB at entry (Al-Orainey et al., 2013). Many of these immigrants live in crowded conditions conducive to TB transmission, have poor diets, and engage in physically stressful manual labour, making them more susceptible to the disease and reactivation of LTBI (Al-Orainey et al., 2013, Almutairi et al., 2018). Moreover, although the government stopped deporting non-Saudis diagnosed with TB, many are still afraid to seek medical services because they fear being dismissed by their employer (Abouzeid et al., 2012, Almutairi et al., 2018).

TB incidence rates in KSA between 1991 and 2010 increased with age and was highest for those older than 45 years (27.4-37/100,000). Children had an incidence of 1.8-2.8/100,000. There was no significant change in TB incidence trend for children and adults younger than 45 years. Those older than 45 showed a significant declining trend over the last 10 years of the study (Al-Orainey et al., 2013). Childhood TB is more reflective of new infections and transmission from adults in the community. BCG vaccination is compulsory at birth in Saudi Arabia, with coverage of 97% of children (Al-Orainey et al., 2013). The fact that TB trend in children did not fall over the 20 years of the study period is an indication of the inability of TB control efforts to reduce the infection rate and halt transmission of the disease in the Kingdom (Al-Orainey et al., 2013).

The high incidence of TB in adults is probably due to reactivation of LTBI (Rajagopalan, 2001). A nationwide community survey of TB done in the early 1990s revealed a high prevalence of LTBI in the Kingdom ranging from 45% in the 25-34 year age group to over 60% in those older than 45 years (al-Kassimi et al., 1993). This large pool of LTBI is likely to be the source of active TB in adults and would explain the high incidence rate of the disease in the older age groups in the country (Al-Orainey et al., 2013, Almutairi et al., 2018).

TB incidence in the Kingdom show clear variation in different regions of the country. A study of TB trends in KSA between 2005 and 2009 found that Makkah, the location of Hajj, had the greatest number of TB cases with the greatest incidence rate in the country (26/100,000 in 2009)(Gleason et al., 2012). Jazan and Riyadh (the capital) had the second and third highest incidence rates for 2009, 18.7/100,000 and 17.7/100,000 respectively. Similarly, a study of TB trends between 2005 and 2012 reported that Makkah had a consistently greater incidence rate over the study period compared with other regions (25.1/100,000; 95% CI= 24.7–25.56) (Almutairi et al., 2018). Riyadh was the region with the second highest incidence rate (17.9/100,000; 95% CI= 17.53–18.27) followed by Jazan (17.1/100,000; 95% CI= 16.31–17.89). Al-Orainey et al. (Al-Orainey et al., 2013) reported on TB trends in the Kingdom between 1991 and 2010 and found that over 70% of the TB cases during the study period were reported from the Central (including Riyadh) and Makkah regions. These two regions have 52% of the population of the Kingdom. Incidence rates for Saudis also showed regional variation. Makkah and Jazan regions showed the highest incidence rate that reached up to 29.5/100,000. The trend rose significantly in Makkah over the study period years. Similarly, the Central region had a significant rise in incidence climbing from 6.4 to 14.2/100,000 over the study period. Other regions showed a much lower and stable incidence of 4-9/100,000 (Figure 4).

The geographical differences in incidence rates in the Kingdom is linked to number of factors. For instance, the reason why Makkah region has a TB incidence rate 2-3 times that of most other regions in the Kingdom is the high proportion of non-Saudis in it (Al-Orainey et al., 2013). They constitute over 40% of the population of the region, many of whom come from countries with high TB incidence rates.

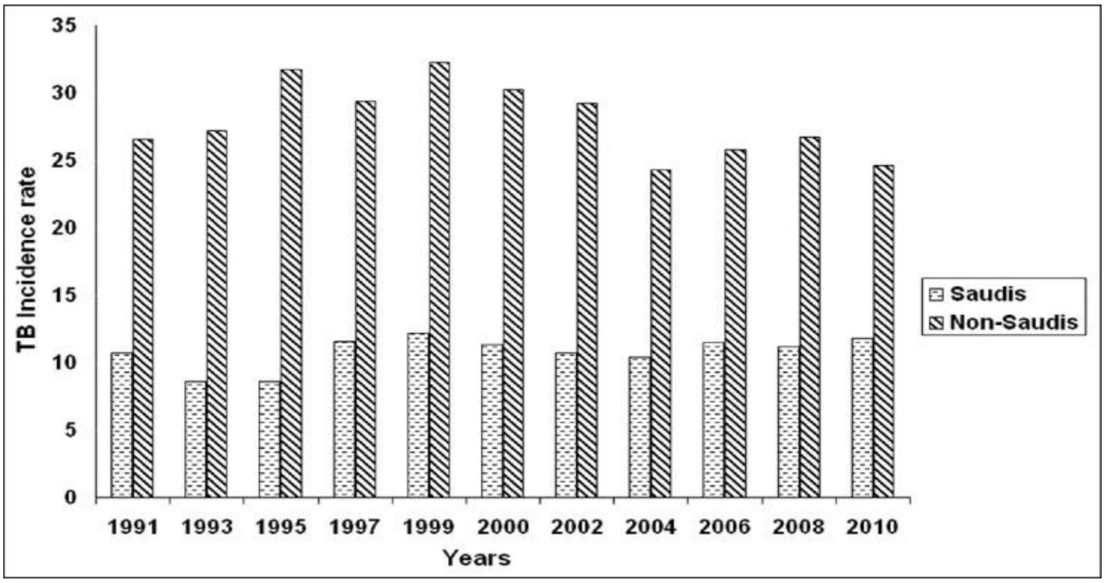
In addition, this region receives more than 10 million foreign visitors every year for pilgrimage (Hajj and Umra), many of them also come from countries with high burden of TB (Al-Orainey et al., 2013, Almutairi et al., 2018). Some of them stay for work in the region. These illegal immigrants tend to live in poor housing conditions and have limited access to health care because of fear of deportation. It is likely that they contribute significantly to the high incidence of the disease in Makkah region (Al-Orainey et al., 2013). Jazan region also has a high incidence rate for TB, more than 2 times the incidence of the rest of the Southern region of the Kingdom (Al-Orainey et al., 2013, Almutairi et al., 2018).This could be attributed to Jazan's proximity to Yemen, which has a high overall TB incidence rate (Almutairi et al., 2018). Jazan is a border area with Yemen and receives many illegal immigrants from that country. Other illegal immigrants land in Jazan by sea from Sudan, Somalia, and other African countries. Like other illegal immigrants, they stay in poor housing conditions and have difficult access to health care which may impact the epidemiology of TB in the region (Al-Orainey et al., 2013). Finally, the high TB incidence rate seen the Central region, including the capital Riyadh could be attributed to a higher frequency of reporting due to the presence of large number of tertiary hospitals that treat patients from all over KSA. In addition, it is a major employment destination for non-Saudis (Al-Orainey et al., 2013, Almutairi et al., 2018).

Data from the Kingdom suggest that the prevalence of MDR-TB is low though there is a higher primary drug resistance. The incidence rate of MDR/RR-TB in the Kingdom in 2017 was 0.36/100,000 and the percentage of TB cases with MDR/RR-TB was 2.6% among new cases and 20% among retreatment (www.who.int/tb/data). In a national, survey conducted between 2009 and 2010, antimicrobial resistance testing was conducted on samples from 1,904 TB patient (Al-Hajoj et al., 2013). The prevalence of resistance to anti-TB drugs were as follows: streptomycin (8.1%; 95% CI= 7.2-9.1), isoniazid (5.4%; 95% CI= 4.7-6.2), rifampin (1%; 95% CI= 0.7-1.3) and ethambutol (0.8%; 95% CI= 0.5-1.2). MDR-TB was found in 1.8% (95% CI= 1.4-2.4) and 15.9% (95% CI= 15.4-16.5) of new and previously treated TB cases, respectively. The study also found that treatment history of active TB, being foreign-born, having PTB, and living in the Western part of the country were the strongest independent predictors of MDR-TB.

In a recent report on MDR-TB among new cases in Medina (a holy city visited by many Hajj and Umrah pilgrims), lower mono-resistance to anti-TB drugs was reported (Elhassan et al., 2017). Resistance to streptomycin, isoniazid, rifampin, ethambutol and pyrazinamide were reported in 1.9%, 1.8%, 1.4%, 1.1% and 2.1% of the isolates respectively. MDR-TB was reported in 4% of the isolates.

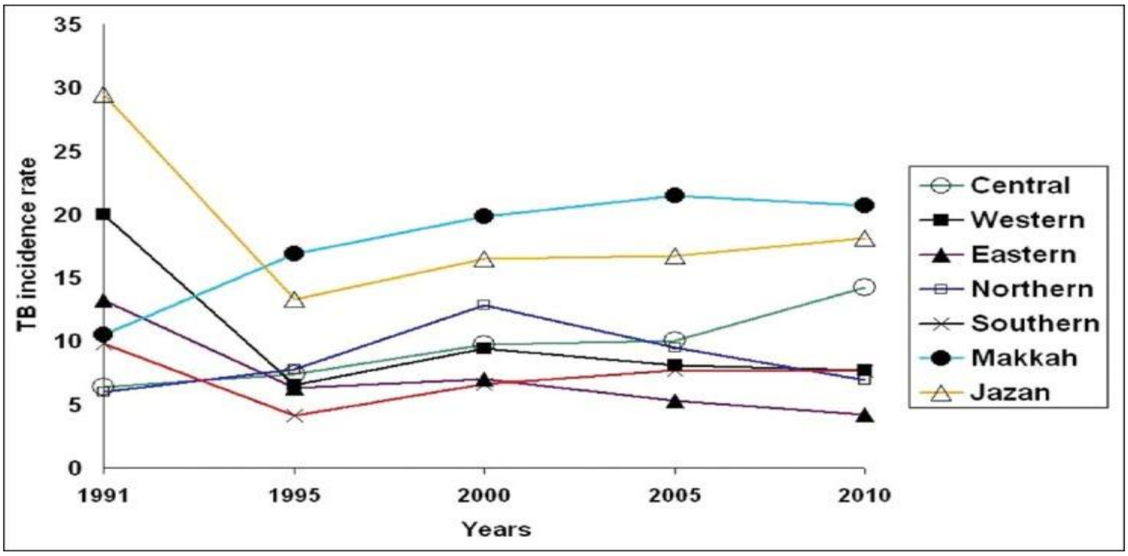
The WHO reported the estimated mortality rate from TB (excluding HIV + TB) to be 3.2/100,000 in Saudi Arabia for 2017, with overall decrease in mortality rates in recent years (www.who.int/tb/data). Abouzeid and colleagues (Abouzeid et al., 2013) investigated mortality among TB patients in Saudi Arabia over a period of 10 years (January 1, 2001, to December 31, 2010). All TB cases registered in Saudi Arabia with known outcome of survival or death while under anti-TB therapy covering the study period were included. The total case fatality rate was significantly higher among Saudis (6.4%) compared to non-Saudis (5.4%). The case fatality rate showed an upward trend starting from the year 2001 reaching a peak in the year 2003 (7.2% and 6.2% among both Saudis and non-Saudis, respectively). Mortality among TB patients showed a declining trend among Saudis starting from the year 2003 and a stagnant trend among non-Saudis. Mortality was positively correlated with advancing age as the rate increased with the increase in age, among both Saudis and non-Saudis. The highest rates were reported among those aged ≥65 years (20.8% among Saudis and 25.2% among non-Saudis). Mortality was correlated with male sex among Saudis (7.3% compared to 5.3% among females), and female sex among non-Saudis (6% compared to 5% among males). Other factors reported to be positively correlated with mortality were prior history of anti-TB therapy, smear positivity, and HIV seropositivity (Abouzeid et al., 2013).

Figure 3. Annual tuberculosis patient numbers and incidence rate* in Saudi Arabia (1991-2010) **



TB=tuberculosis *Incidence rate /100,000 ** From Al-Orainey et al.(Al-Orainey

Figure 4. Tuberculosis incidence rates* and trends for Saudis by region (1991-2010)**



TB=tuberculosis *Incidence rate /100,000 ** From Al-Orainey et al.(Al-Orainey

1.6 Hajj: A risk for tuberculosis and tuberculosis transmission

Hajj represents many of the risk factors for transmission of respiratory infections including TB. The event is one of the largest annual mass gatherings in the world attended by more than 2 million people from more than 180 countries, many of which are endemic for TB. This mass gathering is also characterized by a large elderly population, frequently with underlying health conditions. Extended stays at holy sites, along with physical exhaustion, extreme heat, and the unavoidable overcrowding in housing, ritual sites and transport services, facilitates transmission of infectious agents through shared air and respiratory infections are very common among pilgrims (Ahmed et al., 2006, Gautret et al., 2015). As a consequence, pilgrims attending Hajj maybe at a high risk of acquiring TB infection. Wilder-Smith and colleagues measured the immune response to TB antigens in pilgrims using Quanti-FERON TB assay (Wilder-Smith et al., 2005). They reported that 10% (15/149) of pilgrims who were negative prior to Hajj had a significant rise in the immune response to TB antigens three months after Hajj. This Hajj-related conversion rate (10%) is higher than the reported TST conversion for general long-term travelers to TB high-endemicity countries (Cobelens et al., 2000). Participating in Hajj may also render pilgrims susceptible to reactivation of LTBI due to physical exhaustion, sleep deprivation, poor nutrition, and co-morbid conditions that may lower their immunity (Ai et al., 2016).

Under normal not so crowded circumstances, there are approximately 10 close contacts for each active TB case (Jereb et al., 2003). The situation during the Hajj season is clearly different. Housing areas and ritual sites are excessively congested. Pilgrims remain in close proximity in crowded tents or rooms for several hours per day for several days or weeks. In the holy site of Mina, 50-100 pilgrims share one tent for four days. In Makkah, housing is also overcrowded because of the limited availability of hostels and apartments to accommodate large numbers of pilgrims. Such jammed conditions create bigger numbers of close contacts than usual (Al-Orainey, 2013). Studies have shown that TB infection rate (TST conversion) ranges can be over 50% among closed contacts depending on the closeness to the index case, duration of contact, and prior risk of exposure (Mensah et al., 2017, Morrison et al., 2008). Other factors that may increase the risk of transmission include duration of contact, infectiousness of the patient (that is, being smear positive), and poor ventilation. As most pilgrims travel by air, often for long hours, there is an increased risk of TB transmission from a TB case to the other passengers on board (Centers for Disease and Prevention, 1995, Kenyon et al., 1996).

There are several reports of documented TB infection acquired during air travel particularly on long flights. The risk is greatest for those who sit close to the infectious individual. As such, Hajj may be a risk for developing active TB as well as transmission of TB among national and international pilgrims, among the local population and among Hajj work force as well as a risk for global dissemination of the disease post event.

1.7 Tuberculosis during Hajj

With only one specific large-scale study to ascertain the TB case load in pilgrims during the Haj, (Yezli et al., 2017b), evidence of TB in pilgrims comes mostly from clinical studies of causes of hospital admissions during the Hajj. Alzeer et al.1998, reported that *M. tuberculosis* was the commonest cause of pneumonia requiring hospitalization during the 1994 Hajj. In their study, all pilgrims who failed the first-line of therapy and admitted with pneumonia to 2 hospitals in Makkah during the pilgrimage season between 3-28 May 1994 were investigated. Of the 64 cases included, the causative organism was identified in 46 (73%) patients. *M. tuberculosis* was isolated in 13 (20.3%) of cases making it the most common cause of pneumonia in the study population followed by Gram-negative bacilli (18.8%) and *Streptococcus pneumoniae* (10%). The authors reported that the presentation of *M. tuberculosis*-pneumonia was acute and indistinguishable from pyogenic pneumonia. Thirty-one per cent of tuberculous cases had upper lobe involvement, 54% lower lobe, and 15% multi-lobar, which was similar to the radiographic features in non-tuberculous pneumonia cases. After administration of first-line anti-TB drugs, 92.3% (12/13) of the TB patients recovered.

Madani and colleagues (Madani et al., 2006) performed a cross-sectional study of patients admitted to four hospitals in Mina and three hospitals in Arafat during the 2003 Hajj between 8-14 February. Pneumonia was found to be the most common cause of admission in the 808 patients (19.7%). Open PTB accounted for 5.9% (10 patients) of the 169 cases of pneumonia and 1.2% of all admissions. Mandourah et al. (Mandourah et al., 2012) conducted a cohort study of critically ill Hajj pilgrims over two consecutive Hajj years (18th November to 9th December 2009 and 7th November to 1st December 2010). All patients admitted to the intensive care unit (ICU) for at least 4 hours at 15 hospitals in the cities of Makkah and Medina were included in the study.

Pneumonia was the primary cause of critical illness in 27.2% (123/452) of all ICU admissions during Hajj. Of these, *M. tuberculosis* accounted for 4.9% (6/123) of the cases. Similarly, Asghar et al. (Asghar et al., 2011) conducted a cross-sectional study of pilgrim patients with suspected pneumonia admitted to three tertiary care hospitals in Makkah during the 2005 Hajj (from the 1st to 20th day of the Hajj month of the Islamic year 1426; Jan 2005). While the majority of the 91 pneumonia cases were caused by *Candida albicans* (27.5%) and *Pseudomonas aeruginosa* (20.9%), *M. tuberculosis* was the causative agent in 1 (1.1%) patient. A similar proportion was reported by El-Sheikh et al. (El-Sheikh et al., 1998) who analysed a total of 395 sputum specimens from patients referred to one hospital and 3 dispensaries with symptoms of respiratory tract infections during the 1991 and 1992 Hajj seasons. They reported that 1.2% (5/395) of the samples were positive for TB. While TB is no longer reported as the most common cause of pneumonia in Hajj in recent years, TB cases keep being reported in hospitalised Hajj pilgrims.

TB found in seriously ill patients during Hajj is probably the tip of the iceberg. Cough among pilgrims is very common with rates over 80% having been reported (Deris et al., 2010, Gautret et al., 2015). These patients are often diagnosed with upper respiratory tract infections and only those requiring hospitalization are thoroughly investigate (Al-Orainey, 2013). Hence, undiagnosed TB among non-hospitalised pilgrims could be a serious issue. This was highlighted by Yezli et al. (Yezli et al., 2017b) who conducted a cross-sectional study to evaluate the burden of undiagnosed active PTB in pilgrims arriving in the KSA for the 2015 Hajj. The study enrolled 1,164 non-hospitalised adult pilgrims who had cough and could voluntarily produce sputum samples. Pilgrims were selected from five TB endemic countries in Africa and South Asia. Sputum samples were processed using the Xpert MTB-RIF assay with laboratory results being available for 1,063 samples. Fifteen pilgrims (1.4%) had active previously undiagnosed drug-sensitive PTB (Afghanistan [12; 80%], Pakistan [2; 13.3%], and Nigeria [1; 6.7%]). These TB positive pilgrims pose a risk to other pilgrims from over 180 countries, the local population and may play a role in the international transmission of the disease.

Chapter 2: Active pulmonary tuberculosis among hospitalised and non-hospitalised pilgrims during the Hajj mass gathering

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2.1 Executive summary

Tuberculosis (TB) remains a global public health problem with significant morbidity and mortality. In 2017, the World Health Organisation (WHO) estimated that 10 million people (range, 9.0–11.1 million) developed TB, 9% of whom were infected with the human immunodeficiency virus (HIV). International travel, migration and movement of human populations facilitate the spread of TB. In this context the Kingdom of Saudi Arabia (KSA) is particularly relevant because of its large expatriates' population, mainly from TB-endemic regions, and its yearly hosting of the Hajj and Umrah mass gatherings.

Hajj represents many of the risk factors for transmission of respiratory infections including TB. The event is one of the largest mass gatherings in the world attracting more than 2 million pilgrims from over 180 countries. It is characterized by a large elderly population, frequently with underlying health conditions, many of which originate from low income countries where TB is endemic. Pilgrims gather in close contact to perform physically exhausting religious rites, conditions that facilitate TB transmission.

Little data is available on the prevalence of active or latent TB during Hajj and there have been no specific large-scale controlled studies to define the burden of TB during the event. As pilgrims are not screened before entry to KSA, it is possible that some may enter the Kingdom with active TB and are not diagnosed or treated. This is because respiratory tract infections and cough are common among pilgrims and a proportion of TB cases may not experience symptoms of sufficient severity to prompt health-seeking behavior. In addition, participating in Hajj may also render pilgrims susceptible to reactivation of latent TB infection. The above may lead to TB being missed both among non-hospitalised and hospitalised pilgrims. The current study screened the latter populations to provide the evidence of PTB burden among hospitalised and non hospitalised pilgrims and propose interventions to prevent and control TB in Hajj and other mass gatherings.

Chapter 2: Active pulmonary tuberculosis among hospitalised and non-hospitalised pilgrims during the Hajj mass gathering

For non-hospitalised pilgrims, a large-scale screening for active pulmonary TB (PTB) was conducted among pilgrims attending the 2016 Hajj. The study found that 0.66% of pilgrims with cough from medium/high TB burden countries (mostly from India and Afghanistan) had active PTB. TB prevalence was higher among males, the elderly, those with low level education, those residing in South Asia, those with underlying health conditions, those with previous TB treatment, those coughing for more than a week, those who have contacts diagnosed or treated for TB, those who lived recently in a household with an adult with cough and those who traveled outside their current country of residency in the previous year. However, the difference was not statistically significant with the exception for underlying health conditions and cough duration. Underlying health conditions and cough in the household were independent risk factors for TB after adjusting for other variables.

For hospitalised pilgrims, the study conducted the first screening for active PTB among this population during the 2016 and 2017 Hajj seasons. The study found that 2.9% of inpatients with cough (mostly from Indonesia and India) had active PTB and most (77.7%) of these were missed by the hospitals including MDR-TB cases. TB prevalence was higher among those with no formal education, those residing in Asia, those with underlying health conditions, smokers, those with previous TB treatment, those coughing up blood, those coughing for more than a week and those admitted to an isolation ward. However, the difference was statistically significant only for previous TB treatment and admission ward. Previous TB treatment was independent risk factor for TB after adjusting for other variables.

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.

2.2 Introduction and literature review

A search of electronic databases was conducted for relevant literature in English, without time restriction. Database searched included Pubmed, Scopus and Google Scholar. A combination of the MeSH terms and text words including: “Hajj”, “Pilgrimage”, “Tuberculosis”, “TB”, “Pulmonary”, “Undiagnosed”, “Missed”, “Hospitalised”, “Patient”, “Pilgrim”, “Community” were used. A manual search was also performed reviewing reference lists of identified literature to find additional papers. With few exceptions, only the most relevant and recent publications were used to develop the literature review. Undiagnosed and unreported TB is significant issues that contribute to the transmission of TB and challenge TB control efforts worldwide. Under-diagnosis can occur for reasons such as poor geographical and financial access to health care, lack of or limited symptoms that delay seeking of health care, failure to test for TB when people do present to health facilities, and diagnostic tests that are not sufficiently sensitive or specific to ensure accurate identification of all cases (World Health Organization, 2018b). In 2014, 6 million new cases of TB were reported to WHO, fewer than two-thirds (63%) of the 9.6 million people estimated to have fallen sick with the disease (World Health Organization, 2015b). This means that worldwide, 37% of new cases went undiagnosed or were not reported. In 2017, about 3.6 million (36%) of the estimated 10 million people with TB worldwide were either not reported or not diagnosed (World Health Organization, 2018b). While many of these people are likely to have been treated by public and private providers who are not linked to the National TB Control Programs (NTPs), many would have spent significant amount of time in their community without treatment, increasing the risk of TB transmission.

With respect to Hajj, as pilgrims are not screened before entry to the Kingdom, it is likely that some may enter Saudi Arabia with active PTB. Because respiratory tract infections and cough are common among pilgrims, patients are often diagnosed with upper respiratory tract infections and only those requiring hospitalisation may be thoroughly investigated (Al-Orainey, 2013). This means that potentially many undiagnosed and untreated active PTB cases are brought to the Kingdom and infection could be transmitted to other pilgrims and to local citizens (Yezli et al., 2017b).

Pilgrims infected during the pilgrimage may also spread the infection to contacts in their countries. Transmission of MDR-TB is a real concern as MDR-TB requires long, expensive and extensive treatment with multiple, potentially toxic drugs and outcomes are poor (Orenstein et al., 2009). Also, given the short period pilgrims stay in the Kingdom, short inpatient stay and patients load at healthcare facilities during Hajj, TB cases may be missed among hospitalised pilgrims. This may contribute to poor outcome and represent a potential source of TB infection among pilgrims, other patients and HCWs.

2.2.1 Undiagnosed TB among non-hospitalised populations

Numerous studies from high TB/HIV burden in Africa reported undiagnosed active TB among non-hospitalised individuals in the community. Wood et al.(Wood et al., 2007) conducted a cross-sectional survey of PTB and HIV infection in a sub-Saharan community with high TB/HIV burden but a well-functioning directly observed therapy short course (DOTS) TB control program. Of the 762 participants, TB was diagnosed in 23 (3.3%). Of these, 12 (1.6%) were previously undiagnosed definitive TB cases; 6 (5 HIV-positive) smear-positive cases and 6 (4 HIV-positive) smear-negative/culture positive cases. The study reported that among HIV-positive and -negative individuals, prevalence of notified smear-positive PTB was 1,563/100,000 and 352/100,000, undiagnosed smear-positive PTB prevalence was 2,837/100,000 and 175/100,000, and case-finding proportions were 37% and 67%, respectively. Only 17% of the previously undiagnosed PTB cases reported cough as a symptom. This lack of symptoms suggestive of PTB was thought to be partly responsible for the failure of the passive case-finding DOTS program in adequately identifying PTB cases especially among HIV-positive individuals(Wood et al., 2007).

In a rural community screening of 30,040 adults in Ethiopia in 2009, 482 TB suspects were identified (Deribew et al., 2012). Among the latter, 9 (1.8%) TB cases were detected using smear microscopy and 17 (3.5%) were detected using culture. The prevalence of PTB in the study was 30/100,000 based on smear-microscopy and 76.1/100,000 based on culture. All of the 17 cases detected by culture and 5 cases detected by smear microscopy were new PTB cases. The study reported that there were 4.3 undiagnosed PTB cases for every TB case who was diagnosed through the passive case detection mechanism in health facilities. Among the undiagnosed PTB cases, there were more females than males.

The authors stated that empowerment to seek early health care and low knowledge of women about the cause of TB(Abebe et al., 2010) could have been the reasons for this high number of undiagnosed female TB patients in the community surveyed (Deribew et al., 2012). In a larger national survey among adults in Ethiopia conducted in 2010-2011, the estimated prevalence of smear-positive TB and bacteriologically confirmed TB were 108/100,000 and 277/100,000 (Kebede et al., 2014). A total of 110 bacteriologically confirmed PTB cases were identified including 47 smear-positive cases and 63 smear-negative/culture positive cases. Of the TB cases identified, 37 (79%) smear-positive and 59 (94%) smear-negative, culture-positive cases were new or previously undetected and had not been previously treated. Also, among all confirmed TB cases, more than 50% did not report chronic cough and were identified using chest X-ray screening (Kebede et al., 2014). In 2017, the WHO reports the incidence of TB in Ethiopia as 164/100,000(World Health Organization, 2018b) and the country contributes over 11,000 Hajj pilgrims each year.

A national survey on the prevalence of PTB in the adult population of Tanzania reported a smear-positive TB prevalence of 249/100,000 and a bacteriologically-confirmed TB of 293/100,000. Both of these numbers were higher than previous WHO estimates for the country (Senkoro et al., 2016). Of the 6,302 suspected TB individuals, 154 were bacteriologically confirmed TB cases. Of these, only 5 (3%) were on anti-TB treatment at the time of the survey and 10 (7%) had received previous anti-TB treatment. A similarly high percentage of undiagnosed TB was reported from the first national TB prevalence survey in Zambia (Kapata et al., 2016). The survey was conducted in 2013-2014 and enrolled adult Zambians aged 15 years and above. Among the 46,099 participants, 6,154 submitted at least one sputum specimen for examination. TB was identified in 256/6,123 (4.3%) individuals. The estimated national adult prevalence of TB of all forms and that of smear, culture and bacteriologically confirmed TB were 455 /100,000, 319/100,000, 568/100,000 and 638/100,000 respectively. Importantly, 97% of the TB cases were not on anti-TB treatment at the time of the survey, although 49.7% of the cases that were not on treatment did seek care for their illness. Also, only 61% of the TB cases were symptomatic (Kapata et al., 2016). While the number of Hajj pilgrims from Tanzania and Zambia are relatively low compared to other countries, the high incidence of TB in these countries and the percentage of undiagnosed/unreported cases are concerning.

National TB prevalence surveys from medium-high burden TB countries in Asia also report undiagnosed active TB cases among non-hospitalised individuals in the community (Onozaki et al., 2015). Pakistan has a TB incidence rate in 2017 of 267/100,000(World Health Organization, 2018b). It is one of the largest contributors to the Hajj population with an estimated 160,000 pilgrims each year. A national survey in Pakistan of adults >15 years old in 2010-2011 enrolled 105,913 participants, of whom 10,471 were eligible for sputum examination (Qadeer et al., 2016). The reported prevalence estimates for smear and bacteriologically positive TB were 270/100,000 and 398/100,000 respectively. The survey identified 341bacteriologically positive TB cases of whom 233 had sputum smear-positive TB. Only 61% of the diagnosed TB cases screened positive on symptoms (cough >2 weeks), whereas the other TB cases were detected based on X-ray abnormalities. Importantly, only 7.6% of the 341 participants with bacteriologically positive TB reported to be currently on TB treatment and the ratio of the prevalence of smear-positive TB to the notification rate of new smear-positive TB was 3.1. This suggests significant under detection and under reporting of TB in Pakistan. This was supported by the conclusions of a 2014 study conducted in 12 districts across Pakistan, which estimated the proportion of cases notified to the NTP in the country to be only 32% (Fatima et al., 2014).

Similar observations were reported in prevalence surveys from neighbouring Bangladesh (Onozaki et al., 2015, Zaman et al., 2012, Zaman et al., 2006). The country has a TB incidence rate of 221/100,000 (World Health Organization, 2018b) and a Hajj pilgrims population of around 100,000. Zaman et al. (Zaman et al., 2012) reported the result of TB prevalence survey among 52,098 adult participants from Bangladesh conducted between 2007 and 2009. A total of 33 smear-positive TB cases were detected among the participants giving an adjusted prevalence of 79.4/100,000 (95% CI= 47.1–133.8).At the time of detection, only 3 (9.0%) of the 33 detected cases were under DOTS treatment at a local centre and 18 (54.5%) did not report cough at the time of the survey. These results mirror those of an earlier population-based survey in the rural areas of the country that enrolled 59,395 adults ≥15 years old, 7.1% of whom had cough >21 days (Zaman et al., 2006). Sputum specimens were examined for 3,834 persons, 52 (1.4%) of them were positive for acid-fast bacilli, giving a population-based prevalence rate of smear-positive TB cases of 95/100,000.Around 83% of TB positive cases were either not treated or treated for <1 month with anti-TB drugs before sputum samples were examined (Zaman et al., 2006).

In Vietnam, a national survey among 94,179 adult participant conducted in 2006-2007, reported a prevalence rate of smear-positive TB of 145/100,000 (95% CI= 110-180) assuming no TB in persons aged <15 years (Hoa et al., 2010). Sputum tests were conducted for 7,648 participants and the results of the sputum test, bacterial culture or both, confirmed 269 TB cases, 174 of which were smear-positive. Of the latter, only 6 participants (3.4%) were on TB treatment at the time of the study and 30 (17.2%) had a history of TB treatment. TB symptoms were not apparent in all TB cases. Among the TB cases, productive cough for >2 weeks was reported by 49.6%, any cough for >2 weeks by 54.9%, any cough of any duration by 67.4% and any symptom suggestive of TB by 74.2% (Hoa et al., 2010).

China is another important country with regards to TB and Hajj. The country has a TB incidence rate of 63/100,000, and while it contributes only around 15,000 Hajj pilgrims each year, the country has a high prevalence of MDR-TB among new cases (7.1%) (World Health Organization, 2018b). In 2010, a population-based, cross-sectional survey was conducted among 54,279 adults in Shandong China (Wei et al., 2014). Adjusted prevalence rate of bacteriologically confirmed cases was calculated as 34/100,000. The survey diagnosed 172 new cases, including 19 new bacteriologically confirmed cases (including 11 sputum and culture positive cases, and 8 sputum negative but culture positive cases). A number of these did not report symptoms suggestive of TB. The survey identified only 11 existing cases registered on the national TB program. A larger survey conducted the same year from all 31 mainland provinces in China, enrolled 252,940 participants and examined 9,716 sputum samples (Wang et al., 2014). The survey detected 1,310 cases of active PTB, of which 347 were bacteriologically positive (119/100,000 population; 95% CI= 103–135) and 188 were sputum smear-positive (66/100,000 population; 95% CI= 53–79). The prevalence of smear-positive TB among known cases was only 9/100,000. Earlier national surveys conducted in China in 1990 and 2000 also reported a significant proportion of new undiagnosed and untreated cases of TB identified through the surveys (China Tuberculosis Control, 2004, Wang et al., 2014).

In general, data from countries in Asia report undiagnosed TB and a significant proportion of asymptomatic individuals among TB cases. Onozaki et al. (Onozaki et al., 2015) reported on the national prevalence surveys from 20 countries in Asia between 1990 and 2012. The prevalence of bacteriologically-positive TB disease among adults aged ≥15 years varied widely among countries (120/100,000 population in China in 2010 to 1,500/100,000 population in Cambodia in 2002). Importantly, A high proportion of cases (40-79%) did not report TB symptoms that met screening criteria (generally cough of ≥2–3 weeks, and blood in the sputum) and were only detected due to chest X-ray screening of all survey participants. Also, the ratio of prevalent cases to cases notified to national TB programmes was typically around 2, but was as high as 3 in some counties like Lao PDR and Pakistan (Onozaki et al., 2015).

As per reports from Pakistan, Bangladesh, Vietnam and China, (China Tuberculosis Control, 2004, Fatima et al., 2014, Hoa et al., 2010, Qadeer et al., 2016, Wang et al., 2014, Wei et al., 2014, Zaman et al., 2012, Zaman et al., 2006) data from other Asian countries also report high percentage of undiagnosed, untreated TB cases identified in national TB prevalence surveys. Studies from Cambodia, Republic of Korea, Myanmar, Lao PDR and Thailand, found that only 2-4% of bacteriologically-positive TB cases detected by surveys were on treatment for TB (Onozaki et al., 2015).

2.2.2 Undiagnosed TB among hospitalised populations

Failure to diagnose and adequately treat TB among hospitalised patients could lead to premature death and unrecognized transmission of *M. tuberculosis* (Casey, 1966, 1968, Johnson and Johnson, 1959, Medrano et al., 2014, Rosenthal et al., 1975, von Delft et al., 2015, Whittington, 1983). This puts family members, other patients and the community at increased risk of TB infection and subsequent disease. In addition, the complex contact patterns between health care workers (HCWs) and patients potentiate the spread of TB disease in the healthcare setting, resulting in an increased occupational risk of TB infection and disease among HCWs and practicing medical students (Alele et al., 2018, Boudreau et al., 1997, Sepkowitz, 1994). For example, Medrano and colleagues (Medrano et al., 2014) reported on a case of missed TB that led to widespread transmission in a private hospital in the US. During 2 months in 2010, the hospital identified 38 employees with TST conversions within 6 months of having a negative TST.

Such large number of recently positive TST results within 2 months, with no known explanation, prompted the hospital to investigate the matter. One of the 38 employees, a nurse, was diagnosed with pulmonary TB (PTB) with a matching *M. tuberculosis* genotype and drug resistance pattern to those of a county jail inmate who was also recently diagnosed with pulmonary TB. Although the nurse in question had no known contact with that inmate; another inmate from the same jail had been hospitalised under that nurse's care in 2009. That young man died, and a post-mortem examination result subsequently confirmed TB, which had not been suspected. Exposure to this patient with undiagnosed TB was thought to be responsible for the subsequent widespread transmission. Of the 318 hospital-based contacts without previous positive TST results 87 (27%) were infected, and 9 contacts had active TB (Medrano et al., 2014).

Various studies reported the magnitude of undiagnosed TB among hospitalised patients by analysing autopsy reports (Balabanova et al., 2011, Bobrowitz, 1982, Juul, 1977, Katz et al., 1985, Lee and Ng, 1990, Makela et al., 1971, Roberts et al., 1971, Rosenthal et al., 1975). These studies found substantial numbers of undiagnosed TB cases among patients that were only detected during autopsy examinations. For example, Katz et al. (Katz et al., 1985) reported that during a 21-year period (1960-1980), 82 cases of active TB were diagnosed only at autopsy in patients hospitalised in a medical centre in Israel. They found that around 75% of the patients were over 50 years old and large number of them suffered from accompanying diseases or drug therapy which suppresses the immune system. In 75% of the cases, diagnostic measures for the confirmation of TB were not taken. In another study from a general hospital in Hong Kong, 1,306 autopsy cases were investigated. In these, 63 cases of active TB were identified, 62% of them were only diagnosed at autopsy (Lee and Ng, 1990). A study from a Canadian general hospital reviewed a 6-year period autopsy reports and identified 24 cases of undiagnosed TB (Roberts et al., 1971). These were mostly male, over 60 years old with advanced coexisting disease. Factors reported to have contributed to the failure of diagnosing TB were the short duration of hospitalization, and the masking of signs, symptoms and radiological findings by coexisting disease.

Kilale et al. (Kilale et al., 2013) investigated 74 deceased individuals at a hospital in Tanzania, 34 (45.9%) of whom received diagnosis before death. The main diagnoses were pneumonia 10 (13.5%), heart failure 6 (8.1%), AIDS-related illnesses 6 (6.8%) and malaria 5 (6.8%). They reported that in 24 out of 71 (33.8%) biopsies acid fast bacilli (AFB) were detected.

In Denmark, the incidence of clinically undiagnosed active TB was 0.1% in an autopsy material comprising about 75% of all autopsies carried out in the country between 1969 and 1974 (Juul, 1977). This incidence, corresponded to around one case in every 895 autopsies, mainly among elderly patients from medical units. Similarly, in Birmingham England, among the 14,001 coroner's autopsies performed between 1977 and 1981, 41instances of undiagnosed active TB were identified (Whittington, 1983). These constituted 0.3% of the coroner's post-mortem examinations and 31% of the 132 deaths from TB in Birmingham during the same period. As with other reports, most cases were elderly (20, 48%) and male (29, 71%).

Co-morbidity with other communicable and non-communicable diseases among TB patients is a significant reason for missed TB cases in healthcare facilities. The burden of undiagnosed TB is especially high among patients with HIV and diabetes (Bates et al., 2012). In resource-limited settings of the Americas, south Asia and sub-Saharan Africa, post-mortem studies show that TB accounts for approximately 40% of HIV-related adult deaths and almost half of these TB cases are undiagnosed at the time of death (Gupta et al., 2015). In South Africa, Cohen and colleagues (Cohen et al., 2010)showed that 42% of adults (of whom 94% had HIV) who died in hospital had undiagnosed TB. In another study from the same country, TB was implicated in 67% of deaths among HIV-positive patients but a third of infections were clinically unsuspected (Wong et al., 2012).

Screening of outpatients in South Africa with HIV infection for undiagnosed TB has shown rates of 12-20% (Bassett et al., 2010, Kufa et al., 2012, Lawn et al., 2011). In West Africa, screening for active TB before INH preventive therapy among HIV-infected adults found that 1.6% of adults considered free of active TB based on clinical screening, actually had active TB (Moh et al., 2017). In India, the prevalence of undiagnosed TB among HIV patients was reported as 0.84% among adults and 0.47% among children (Padmapriyadarsini et al., 2016). Mntonintshi et al. (Mntonintshi et al., 2017) reported that TB is missed even among HIV patients who present with severe anaemia, although TB is a major cause of severe anaemia among this population. In one hospital, 50 patients with HIV infection and severe anaemia who after treatment was not investigated for TB were recruited for the study. Of the participants, 40 (80%) had a positive TB symptom with one or more symptoms and 6 (12%) patients had physical signs suggestive of extra-PTB that were not noted by the doctors who first assessed them.

The overall prevalence of TB was 86%: 43 patients (86%) had either or both bacteriological and clinical TB, 42 (84%) had clinical TB and 14 (28%) had bacteriologically proven TB (Mntonintshi et al., 2017)

Bates and colleagues reported on the burden of unsuspected PTB and co-morbidity with other diseases among sputum producing adult inpatients in a tertiary referral centre in Zambia (Bates et al., 2012). The study recruited newly admitted patients who were screened for PTB using fluorescent smear microscopy and automated liquid culture. The burden of PTB, unsuspected TB, TB co-morbidity with non-communicable and communicable diseases was determined. Of the 900 inpatients involved (70.6% HIV infected, 30.8% non-TB suspects, 31.8% TB suspects and 37.4% already receiving TB treatment), 202 (22.4%) had culture confirmed TB. Among the latter, 27 (13.4%) TB cases were unsuspected on admission and would probably have remained undiagnosed if not actively screened on this study. Also, there were 18 confirmed cases of MDR-TB, 5 (27.7%) of which were unsuspected. Moreover, roughly half the TB cases were co-morbidities with other communicable and non-communicable diseases. Within the latter group, there was a significantly higher likelihood of TB co-morbidity in patients with renal disorders and those with diabetes compared to other non-communicable diseases patients. Such association has been documented by others (Creswell et al., 2011, Young et al., 2009). These two patient groups also featured prominently in the unsuspected TB cases, indicating that these non-communicable diseases presentations are possibly masking TB and contributing to missed cases (Bates et al., 2012).

With respect to Hajj, as pilgrims are not screened before entry to the Kingdom, it is likely that some may enter the Kingdom with active PTB. Because respiratory tract infections and cough are common among pilgrims, patients are often diagnosed with upper respiratory tract infections and only those requiring hospitalization may be thoroughly investigated (Al-Orainey, 2013). TB cases have been identified among inpatients during Hajj with TB being reported as a major cause of pneumonia at the event (Alzeer et al., 1998, Madani et al., 2006). Also, given the short period pilgrims stay in the Kingdom, short inpatient stay and patients load at healthcare facilities during Hajj, TB cases may be missed. This may contribute to poor outcome and represent a potential source of TB infection among pilgrims, other patients and HCWs.

2.3 Aim and objectives

The overall aim of this study was to determine the occurrence of active PTB (both sensitive and MDR) among hospitalised and non-hospitalised pilgrims during Hajj mass gatherings.

2.3.1 Tuberculosis among non-hospitalised pilgrims

Specific objectives:

- To investigate active PTB (both sensitive and drug-resistant) among non-hospitalised pilgrims with cough from medium and high burden TB countries regardless of health status
- To investigate factors associated with active PTB among non-hospitalised pilgrims during Hajj
- To describe the cases of active PTB among non-hospitalised Hajj pilgrims identified in the study
- To propose recommendations for interventions to improve TB case detection, heath-seeking behavior among pilgrims and prevention and control of TB during Hajj

2.3.2 Tuberculosis among hospitalised pilgrims

Specific objectives:

- To investigate active PTB (both sensitive and drug-resistant) among hospitalised pilgrims with cough regardless of their admission diagnosis
- To investigate factors associated with active PTB among hospitalised pilgrims during Hajj
- To describe the cases of active PTB among hospitalised Hajj pilgrims identified in the study
- To propose recommendations for interventions to improve TB case detection, heath-seeking behavior among pilgrims and prevention and control of TB during Hajj

2.4 Methods

2.4.1 Tuberculosis among non-hospitalised pilgrims

2.4.1.1 Study design

The study was a prospective cross-sectional design study to investigate active PTB among non-hospitalised pilgrims symptomatic for cough during the Hajj.

2.4.1.2 Study location

The study was conducted in Makkah, KSA, the site of the Hajj religious mass gathering.

2.4.1.3 Study period

The study was conducted over roughly a one-month period (Hajj month) between 5thSeptember 2016 and 1st October 2016 (4th-30th Dull Hija 1437H in the Islamic calendar).

2.4.1.4 Study population

2.4.1.4.1 Sample size

Pilgrims were enrolled from 16 selected countries in African, South Asia and the former Soviet Union. They were enrolled in the study if they had cough and could voluntarily produce sputum samples. The countries were chosen based on their TB endemicity (medium to high), prevalence of MDR-TB and the number of pilgrims coming from each country to Hajj each year (Table 1). Emphasis was on countries endemic for TB, with high MDR-TB rates and large pilgrims' populations.

The estimated number of Hajj pilgrims in 2016 was around 2 million, and it is estimated that over 80% of pilgrims develop cough during Hajj (Gautret et al., 2015). Previous data from Hajj(Yezli et al., 2017b) suggest that the prevalence of active TB among non-hospitalised pilgrims with productive cough is 1.4%. The sample size was determined using Epi Info version 7[ref] using a margin of error of 0.5%, a confidence interval (CI) of 95%, and a population size of 1,600,000 people. The minimum sample size estimated for the study was 2,118. To account for losses, a larger sample size of 2,451 pilgrims was enrolled in the study.

2.4.1.4.2 Eligibility criteria

Inclusion criteria

Inclusion criteria for the study were as follows:

- Consenting adults (>18 years old)
- Male and female
- Hajj pilgrims
- From the selected countries (Table 1)
- Non-hospitalised, regardless of health status
- With cough
- Can voluntarily produce sputum samples

Exclusion criteria

Exclusion criteria for the study were as follows:

- Non-pilgrims
- Pilgrims <18 years of age
- Pilgrims who refuse to give consent for the study
- Pilgrims asymptomatic of cough or those incapable of producing sputum
- Pilgrims not from the selected list of countries (Table 1)

2.4.1.5 Recruitment process

Consenting adult pilgrims who have cough and can voluntarily produce sputum samples were recruited during the study period from selected countries (Table 1) irrespective of their health status. Data and sputum samples were collected from enrolled pilgrims. Data was collected via specifically formulated form (see Appendix 1: Data collection form for non-hospitalised pilgrims symptomatic for cough). The data collection form was developed after literature reviews on TB risk factors and was adopted for the context of Hajj. Data collected include contact information, demographics and TB risk factors information (i.e. age, gender, country of origin, level of education, occupation, smoking habits, underlying health conditions and travel history) as well as previous TB history or treatment.

The study was conducted in Makkah over the Hajj month mainly in the site of the accommodation of the pilgrims from the selected countries. This was done at times when the pilgrims were free and relaxed avoiding times/dates when pilgrims were busy, under time pressure, on the move or involved in Hajj rituals. Hence, recruitment was mainly done during the afternoon/evening at the place of residence of the pilgrims.

The research assistants (volunteers from Global Center for Mass Gatherings Medicine (GCMGM), Makkah hospitals and medical students) coordinated with the "mutawifs" (personnel from the country of origin of the pilgrims who accompany the pilgrims from their own country and assist them through the Hajj process until returning to their home countries. The mutawifs are an important source of information on the pilgrims' activities, movements and whereabouts during Hajj. They also speak the pilgrims' native tongue and can assist in facilitating communication with and access to pilgrims from a particular country.

PI and study team had determined the appropriate time to approach Mutawifs with medical missions' support. The study PI conducted training sessions (workshops) aimed to explain the aim of the study, objectives and Mutawifs' role during data collection as well as emphasized on patients' information confidentiality.

The research assistants approached pilgrims from selected countries at random, introduce themselves and tried to locate those with cough. Research assistants approached these symptomatic pilgrims and explain the study and obtained consent before enrolment in the study. Recruitment continued until the target sample size was reached. Infection control measures were reviewed by all the study team that were in contact with pilgrims. Data collectors wore a mask during data collection. Sample collectors wore personnel protective equipment and washed their hands before and after sputum sample collection.

2.4.2 Tuberculosis among hospitalised pilgrims

2.4.2.1 Study design

The study was a prospective cross-sectional design study to investigate active PTB among hospitalised pilgrims symptomatic for cough during the Hajj.

2.4.2.2 Study location

The study was conducted in Makkah, KSA, the site of the Hajj religious mass gathering. It comprised 13 hospitals situated in the city comprising Hajj holy sites, including temporary hospitals operational only during Hajj days, as shown in Table 2.

2.4.2.3 Study period

The study was conducted during the Hajj lunar month (1st-30thDulHija) during the 2016 and 2017 Hajj seasons, corresponding to 2nd September-1st October 2016 and 22nd August-21st September 2017, respectively.

2.4.2.4 Study population

2.4.2.4.1 Sample size

The study enrolled hospitalised pilgrims admitted to the selected healthcare facilities (Table 2) during the study period if they had cough and could voluntarily produce sputum samples or respiratory samples could be obtained from standard patient care. The patients were enrolled irrespective of their admission diagnosis or cause of hospitalization.

It is estimated that around 4,800 pilgrims were hospitalised in the 2015 Hajj month. Also, respiratory tract infection and pulmonary diseases are reported to account for up to 40% of hospital admissions in Hajj (Madani et al., 2006). Hence, the estimated study pool number was 1,920. The prevalence of undiagnosed PTB among hospitalised Hajj pilgrims is unknown. However data from other settings suggest that around 3% of hospitalised patients with suggestive symptoms have active PTB (Assefa et al., 2019). We aimed to enroll all patients that fulfilled the inclusion criteria in our study, however a minimum sample size for the study was calculated as follows: The sample size was determined using Epi Info version 7[ref] using a margin of error of 2%, a confidence interval (CI) of 95%, a study population size of 1,920 patients and a TB prevalence of 3% among the hospitalised patients. The minimum sample size estimated for the study was 245. A larger sample size of 347 pilgrims was enrolled in the study.

2.4.2.4.2 Eligibility criteria

Inclusion criteria

Inclusion criteria for the study were as follows:

- Consenting adults (>18 years old)
- Male and female
- Hajj pilgrims
- From the selected healthcare facilities (Table 2)
- Hospitalised, regardless of admission diagnosis
- With cough
- Can voluntarily produce sputum samples or respiratory samples can be obtained from standard patient care.

Exclusion criteria

Exclusion criteria for the study were as follows:

- Non-pilgrims
- Patients <18 years of age
- Patients who refuse to give consent for the study or consent could not be obtained
- Patients asymptomatic for cough, those incapable of producing sputum and cases where respiratory samples could not be obtained under standard patient care
- Patients not from the selected healthcare facilities (Table 2)

2.4.2.5 Recruitment process

Research assistants used hospital logbooks, admission information and information from the public health surveillance teams operational during Hajj to locate newly admitted patients to the healthcare facilities and asses their eligibility for the study. The research team then approached the patients at an appropriate time to minimize any effect on patient care. They introduce themselves explain the study and obtained consent before enrolment in the study. For severely ill patients, consent was obtained from eligible person and data was collected from the patient guardian/escort and other sources (e.g. clinicians and clinical records). Infection control measures were reviewed by all the study team that were in contact with patients and were implemented during the data and samples collection. This included wearing appropriate personal protective equipment and adherence to hand hygiene policies.

Data and sputum samples were collected from enrolled patients. Data was collected via specifically formulated form (see Appendix 2: Data collection form for hospitalised pilgrims symptomatic for cough). The data collection form was developed after literature reviews on TB risk factors and was adopted for the context of Hajj. Data collected include contact information, demographics and TB risk factors information (i.e. age, gender, country of origin, level of education, occupation, smoking habits, underlying health conditions and travel history) as well as previous TB history or treatment. Clinical data relating to the patients was also collected, including the admission date, ward and diagnosis, duration of illness, TB screening and results, treatment, final diagnosis and hospitalization outcome.

2.4.3 Data collection

- The data collection tools were carefully designed according to the study objectives and reviewed to ensure good understanding of questions and acquiring clear and precise answers.
- Questions were developed to be as precise and unambiguous as possible with emphasis on multiple choices and close-ended questions for accuracy.
- Study questionnaires were translated to Arabic using a professional certified medical translator. Translated materials were back-translated by someone else other than the first translator to make sure that the translation is as accurate as possible.
- Study tools were tried and tested prior to the actual date of data collection in places different from the sample settings. Final versions of research tools were revised carefully.
- Clear step by step study instructions were produced and distributed to the research assistants in Arabic and English so that they maintain a uniform standard way of collecting the data.
- The information sheets as well as the consent statement were also translated into Arabic using a professional certified medical translator. Translated materials were back-translated by someone else other than the first translator to make sure that the translation is as accurate as possible.
- Researchers conducted interviews in English or Arabic or any other language they master from the participants nationalities. Assistance from the Mutawifs was used to ensure accurate data collection and clear communication with pilgrims. This was important especially in cases of illiterate pilgrims.
- The data collected and the quality of the information gathered was reviewed at the end of each day of the study to identify possible issues and improve data quality going forward.
- Training in research methods was provided by the principal investigator for the study team to ensure that they understood the study collecting tools and research objectives. This included the way to conduct the face-to-face interviews.
- The study team was given training on Good Clinical Practice (GCP) and informed consent before starting the data collection.

2.4.4 Data entry and cleaning

Data was entered following the gold standard for professional data entry which is double data entry. Data was entered twice in Excel and the two data sets were then compared, differences were examined, errors were verified against the original questionnaires and corrections were made. The data set was then exported to SPSS software where frequencies for all variables were generated. The frequency tables generated were then examined to detect unusual values. Final databases were cleaned by the principle investigator to ensure quality before analysis.

2.4.5 Sample collection and processing

Sputum samples were collected in sterile containers from each participant at the time of enrolment. Sputum samples were transported in cold conditions (2-8 °C) to the laboratory within 24 hours of collection. Once received the samples were stored at -80°C to avoid degradation of DNA until processing. All sputum samples were processed at the Haddah Regional Laboratory (Makkah) after Hajj using the Xpert MTB/RIF assay as described previously (Helb et al., 2010). Briefly, sample reagent was added at a 1:3 ratio to sputum samples (i.e, 0.5 mL of sputum sample to 1.5 mL of the sample reagent) and vortexed every 5 min during a 15-min incubation period at room temperature. Then, 2 mL of the inactivated sample mixture was transferred to the Xpert MTB/RIF assay cartridge and processed in the GeneXpert machine in accordance with manufacturer's instructions (Cepheid, Sunnyvale, CA).

In December 2010, the WHO endorsed the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) for the rapid diagnosis of TB and MDR-TB (World Health Organization, 2010b) The test is recommended for use in individuals suspected of MDR-TB or HIV-associated TB (World Health Organization, 2010b). The Xpert MTB/RIF assay is capable of detecting the *M. tuberculosis* complex while simultaneously detecting rifampicin resistance in <2 hours (O'Grady et al., 2011). The detection of rifampicin resistance is considered a proxy marker for MDR-TB, as an estimated 90% of rifampicin-resistant *M. tuberculosis* isolates are also resistant to isoniazid (Chang et al., 2012, Van Rie et al., 2010). The assay has been successfully evaluated and used in a number of studies for identifying unsuspected TB among hospitalised and non-hospitalised patients (Bates et al., 2013, Bates et al., 2012, O'Grady et al., 2012, Yezli et al., 2017b).

2.4.6 Data analysis

Characteristics of the study population were summarized as frequencies, percentages calculated for categorical variables and as means, range and standard deviations (SD) for quantitative variables. The association between demographic and clinical variables and TB was evaluated by Chi square test or Fisher exact test as appropriate. In addition, odds ratios (ORs) and their CIs were calculated. Multiple logistic regression analysis, using penalized likelihood (Firth method), were performed to examine the potential impact of the variables that were identified as being significant at 0.25 in the bivariate analysis. All of the tests for significance were two-sided and p values < 0.05 were considered statistically significant. All analysis were done using SPSS 22.0 (SPSS Inc., Chicago, USA) and SAS 9.4 (SAS Institute Inc., NC, USA) software program.

2.4.7 Ethics

The study was approved by the King Fahad Medical City Ethics Committee and the Institutional Review Board (IRB log: 16-329E) (Appendix 5) and by Liverpool School of Tropical Medicine (LSTM) research Ethics Committee (19-084). The study was conducted in accordance with the Ethics Committee's guidelines. Prior to enrolment in the study, each volunteer was informed in detail about the protocol purpose and procedures and the risks and discomforts to be expected. Verbal consent was obtained from each volunteer and the person explaining and obtaining the consent signed and dated the data collection form. When a patient was illiterate or could not understand the consent statement due to language barrier, the consent statement was explained in his/her native language via Mutawif, the medical representative or a peer/accompanying pilgrim. The information sheet and informed consent statement were distributed to the participant to read and ask any questions and the content was explained to them. Participants were told that they were free to withdraw their consent and to discontinue participation at any time without prejudice or loss of benefits to which they are otherwise entitled. The consent statement form had the name and contact details of a study representative so that participants had the opportunity to ask further questions if they needed to.

2.4.8 Confidentiality

The importance of privacy and confidentiality of participants was highlighted to the study team. Data i.e. human subjects, questionnaires and data collection forms, specimens, and laboratory data was linked using a unique patient identification number assigned upon enrolment. All relevant data and documents were secured in locked cabinets and/or password-protected files; with access given to selected research personnel.

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	221	1.6	102,795
India	204	2.8	149,008
Indonesia	319	2.4	169,996
Malaysia	93	1.5	24,412
Pakistan	267	4.2	160,611
North Africa			
Algeria	70	2.5	30,177
Morocco	99	1.0	31,219
Ethiopia	164	2.7	11,684
Nigeria	219	4.3	75,212
Somalia	266	8.7	2,435
Sudan	77	2.9	27,490
South Africa	567	3.4	2,435
Former Soviet countries			
Tajikistan	85	20	3,353
Kazakhstan	66	26	2,729
Kyrgyzstan	144	26	1,993

*2017 data (www.who.int/tb/data) RR-TB=rifampicin-resistant tuberculosis (TB) MDR-TB=multidrug-resistant TB

Table 2. Characteristics of the hospitals included in the study

Hospital name	Operational period	# of medical staff	# of beds	#ICU beds	# isolation rooms
Holy sites hospitals					
Arafat General Hospital	7 days	406	300	28	1
East Arafat Hospital	7 days	397	236	52	29**
Mina Emergency Hospital	19 days	483	190	34	6
Mina Al-Wadi Hospital	19 days	553	160	25	12
Mina Al-Jisr Hospital	7 days	413	150	28	3
Alrahmah Mountain Hospital	7 days	312	140	17	2
Namera Hospital	7 days	281	90	12	1
Mina New Street Hospital	**7 days**	**287**	**50**	**16**	**12**
Other Makkah hospitals					
Alnoor Specialist Hospital	All year	1900	500	65	37*
King Faisal Hospital	All year	935	200	36	10*
Ajyad Emergency Hospital	All year	218	20	20	1*
King AbdulAziz Hospital	All year	1142	300	30	15*
Hera General Hospital	All year	925	279	28	17*

** 9 negative pressure room and 20 others *Negative pressure room ICU=intensive care unit

2.5 Results

2.5.1 Tuberculosis among non-hospitalised pilgrims

The study enrolled 2,451 pilgrims symptomatic for cough of any duration. Of these 939 (38.3%) produced saliva samples and hence were excluded from the study (Figure5). The remaining 1,512 pilgrims were able to produce sputum samples, and these were tested using the MTB/RIF assay. Two samples showed invalid results and were excluded from the analysis. Hence, overall 1,510 pilgrims with valid sputum sample results were included in the study and the analysis.

2.5.1.1 Characteristics of the study population

Pilgrims originated from 16 countries in Africa, former Soviet countries and South Asia. These countries have medium/high TB burden and the former Soviet countries (Tajikistan, Kazakhstan, Kyrgyzstan) in particular have high prevalence of MDR/RR-TB among new TB cases (Table 1). Many of the countries included in the study (e.g. Bangladesh, India, Indonesia, Pakistan and Nigeria) also contribute a considerable number of pilgrims to the total Hajj population (Table 1).

However, pilgrims were resident (for at least the previous year) in 19 countries, mainly India (15.23%), Bangladesh (14.77%) and Ethiopia (11.85%). In general, nearly half (48.71%) of the pilgrims were residing in South Asia.

The characteristics of the study population are summarized in Table 3 and Figures6-9. The highest number of respondents came from India; 230(15.2%) whereas only 6 (0.40%) were from Kyrgyzstan. The mean age of the study population was 56.1 (SD= 12.9 years, range= 19-90 years) with a male: female ratio of 2.6:1. Nearly 61% of the respondents had no formal education and 22.1% declared having an underlying health condition. Hypertension and diabetes were the most common co-morbidities identified represent respectively in 56.1% and 42.6% of those with underlying health conditions (Table 4). Similarly, 21.9% reported that they were taking medications at the time of the study. One pilgrim from Sudan declared that she was pregnant at the time of enrolment in the study.

Nearly 16% of the respondents declared that they were smokers of tobacco products such as cigarettes, cigars or pipes or have smoked such products in the past. However, only 7.43% declared they were current smokers at the time of the study (Table 3). A small minority (3.63%) of the respondents had occupations associated with increased risk of TB infection (Table 3). Travel information indicated that 82 (5.63%) respondents have traveled outside their country of residence in the previous year visiting countries in Africa, Asia, the Middle East, Europe and Australia. The most common destinations visited were KSA (48.78%), Pakistan, (18.29%), India (9.75%), United Arab Emirates (7.31%) and Thailand (7.31%). The purpose of visiting KSA in the previous year was probably to perform Umrah/Hajj, as all pilgrims (40/1510, 2.83%) who reported visiting KSA also reported performing Umrah/Hajj in the previous year.

At the time of recruitment, most pilgrims (85.66%) reported a cough of one week or less in duration. Thirty pilgrims (2.14%) declared that they were coughing blood and 161 (15.66%) stated that within the previous month they shared the household with an adult with a cough (Table 3). A minority of respondents (1.91%) stated that they have had a close contact diagnosed or treated for TB. While no pilgrim declared that they were receiving TB treatment at the time of enrolment, 8 (0.61%) revealed that they had been treated for TB in the past, 7 of whom confirmed that they had completed their TB treatment.

However, the reported TB treatment duration was over 6 months in only 6 cases while the other 2 cases reported treatment duration below 6 months (Table 3). Around 38% (3/8) of those previously treated for TB originated from Bangladesh and the rest were nationals of Morocco, India, Pakistan and Afghanistan.

Figure 5. Flow chart of the non-hospitalised pilgrims study enrolment and results (By author)

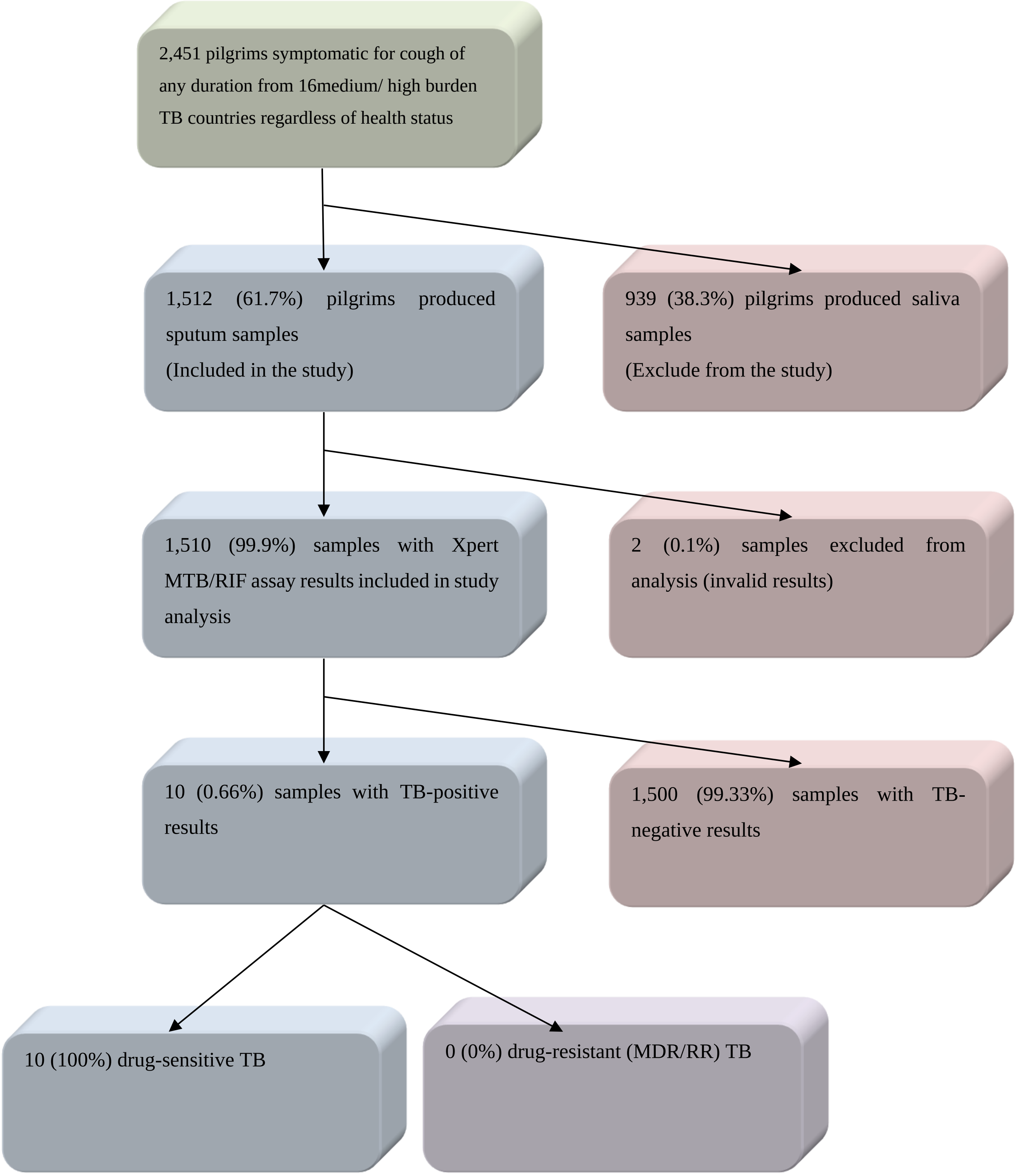


Table 3. Characteristics of the enrolled pilgrims' population

Variable	Number (n)	Percentage (%)
Pilgrims enrolled	**1510**	
Gender	**1458**	
Male	1050	72.02
Female	408	27.98
Age	**1351**	
Mean (Range)	**56.1 (19-90)**	
≤47	328	24.28
>47-55	266	19.69
>55-64	384	28.42
>64	373	27.61
Nationality	**1509**	
Afghanistan	88	5.83
Algeria	60	3.98
Bangladesh	223	14.78
Ethiopia	179	11.86
India	230	15.24
Indonesia	44	2.92
Kazakhstan	65	4.31
Kyrgyzstan	6	0.40
Malaysia	33	2.19
Morocco	50	3.31
Nigeria	40	2.65
Pakistan	118	7.82
Somalia	102	6.76
South Africa	35	2.32
Sudan	94	6.23
Tajikistan	142	9.41
Country of residence in past year	**1510**	
Afghanistan	88	5.83
Algeria	60	3.97
Bangladesh	223	14.77
Egypt	1	0.07
Ethiopia	179	11.85
India	230	15.23
Indonesia	43	2.85

Cont…. Table 3. Characteristics of the enrolled pilgrims' population

Variable	Number (n)	Percentage (%)
Kazakhstan	65	4.30
Kyrgyzstan	6	0.40
Malaysia	33	2.19
Morocco	50	3.31
Nigeria	40	2.65
Pakistan	117	7.75
Qatar	1	0.07
Saudi Arabia	1	0.07
Somalia	102	6.75
South Africa	34	2.25
Sudan	95	6.29
Tajikistan	142	9.40
Region lived in in the past year	**1507**	
South Asia	734	48.71
Former Soviets	213	14.13
Other African Countries	355	23.56
North Africa	205	13.60
Level of education	**1449**	
No formal education	878	60.59
Primary education	202	13.94
Secondary education	199	13.73
University-higher education	170	11.73
Occupation	**1433**	
Health care worker	6	0.42
Miner	37	2.58
Laboratory personnel	1	0.07
Refugee camp worker	6	0.42
Prison staff	2	0.14
None of the above	1381	96.37
Pregnancy	**1473**	
Yes	1	0.06
No	407	27.63
NA (male)	1065	72.31
Underlying health conditions	**1443**	
Yes	319	22.11

Cont.… Table 3. Characteristics of the enrolled pilgrims' population

Variable	Number (n)	Percentage (%)
No	1124	77.89
Chronic kidney disease	**1443**	
No	1436	99.51
Yes	7	0.49
Chronic liver disease	**1443**	
No	1440	99.79
Yes	3	0.21
Chronic lung disease	**1443**	
No	1426	98.82
Yes	17	1.18
Cardiovascular disease	**1443**	
No	1423	98.61
Yes	20	1.39
Hypertension	**1443**	
No	1264	87.60
Yes	179	12.40
Cancer	**1443**	
No	1442	99.93
Yes	1	0.07
Immunosuppressive illness	**1443**	
No	1442	99.93
Yes	1	0.07
Diabetes	**1443**	
No	1307	90.58
Yes	136	9.42
Stroke	**1443**	
No	1443	100.00
Not Listed	**1443**	
No	1368	94.80
Yes	75	5.20
Travel outside current country of residence in the past year	**1456**	
Yes	82	5.63
No	1374	94.37

Cont.… Table 3. Characteristics of the enrolled pilgrims' population

Variable	Number (n)	Percentage (%)
Hajj/Umrah (Past-year)	**1510**	
No	1375	97.17
Yes	40	2.83
Smoking (Current)	**1510**	
No	1370	92.57
Yes	110	7.43
Past smoking	**1510**	
No	1231	90.71
Yes	126	9.29
Any medication	**1510**	
No	1136	78.02
Yes	320	21.98
Previous TB treatment	**1510**	
No	1295	99.39
Yes	8	0.61
TB treatment duration	**1510**	
1 month	1	12.50
2-5 months	1	12.50
6-12 months	5	62.50
12 months	1	12.50
TB treatment completed	**1510**	
Yes	7	100.00
Current TB treatment	**1510**	
No	17	100.00
Cough in household	**1510**	
No	867	84.34
Yes	161	15.66
Close contacts TB patient	**1510**	
No	1232	98.09
Yes	24	1.91
Cough up blood	**1510**	
No	1375	97.86
Yes	30	2.14

Cont.… Table 3. Characteristics of the enrolled pilgrims' population

Variable	Number (n)	Percentage (%)
Cough length (Days)	**1510**	
<= 1 Week	1195	85.66
>1 to 2 Weeks	84	6.02
>2 to 3 Weeks	42	3.01
> 3 Weeks	74	5.30

TB; Tuberculosis, NA; not applicable

Table 4. Underlying health conditions among enrolled pilgrims

Underlying health conditions	n= 319	Percentage (%)
Hypertension	179	56.11
Diabetes	136	42.63
Chronic kidney disease	7	2.19
Chronic lung disease	17	5.33
Chronic liver disease	3	0.94
Cardiovascular disease	20	6.27
Stroke	0	0.00
Cancer	1	0.31
Immunosuppressive illness	1	0.31
Other	75	23.51

Figure 6. Pilgrims by age

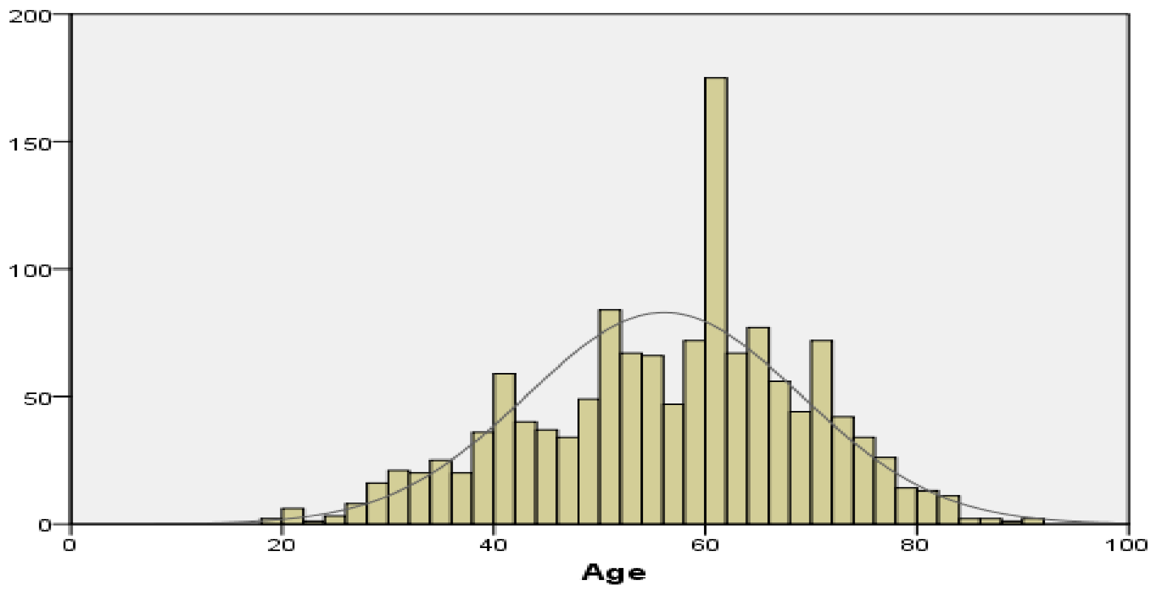


Figure 7. Pilgrims by age group

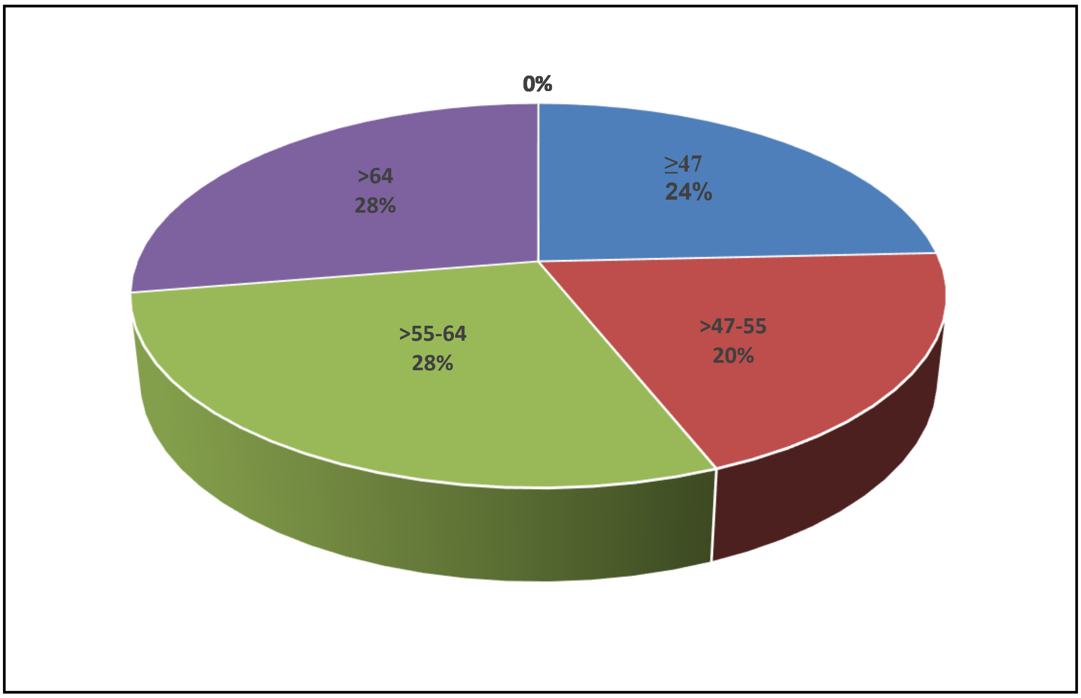


Figure 8. Pilgrims by country of origin

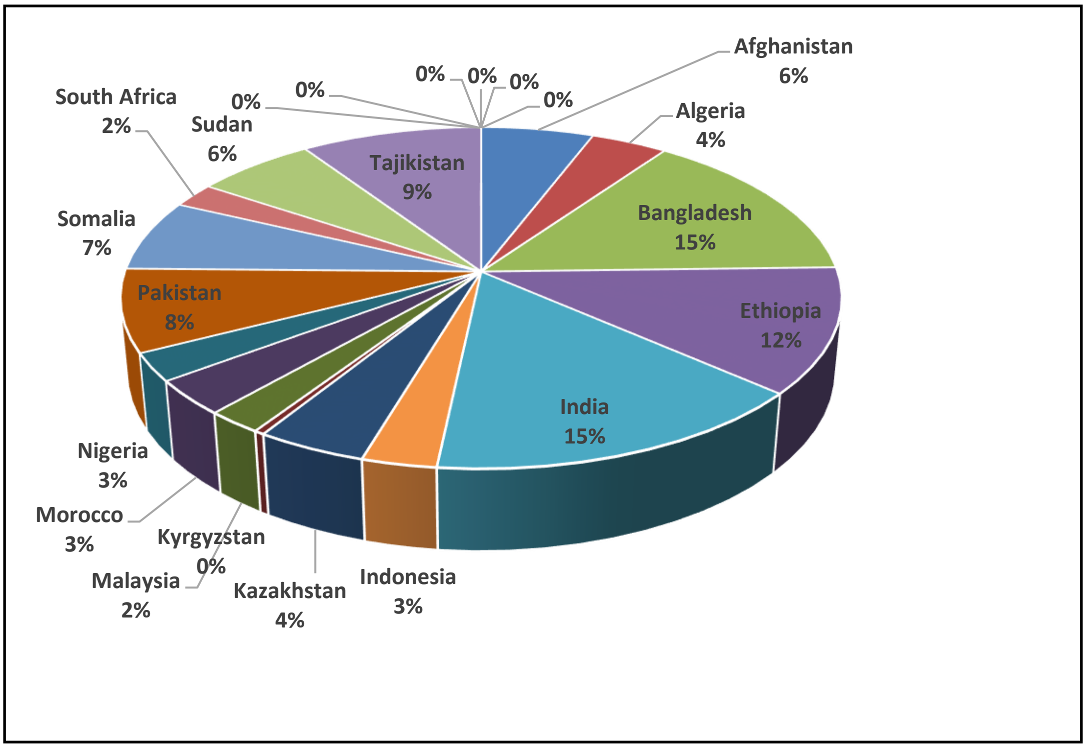
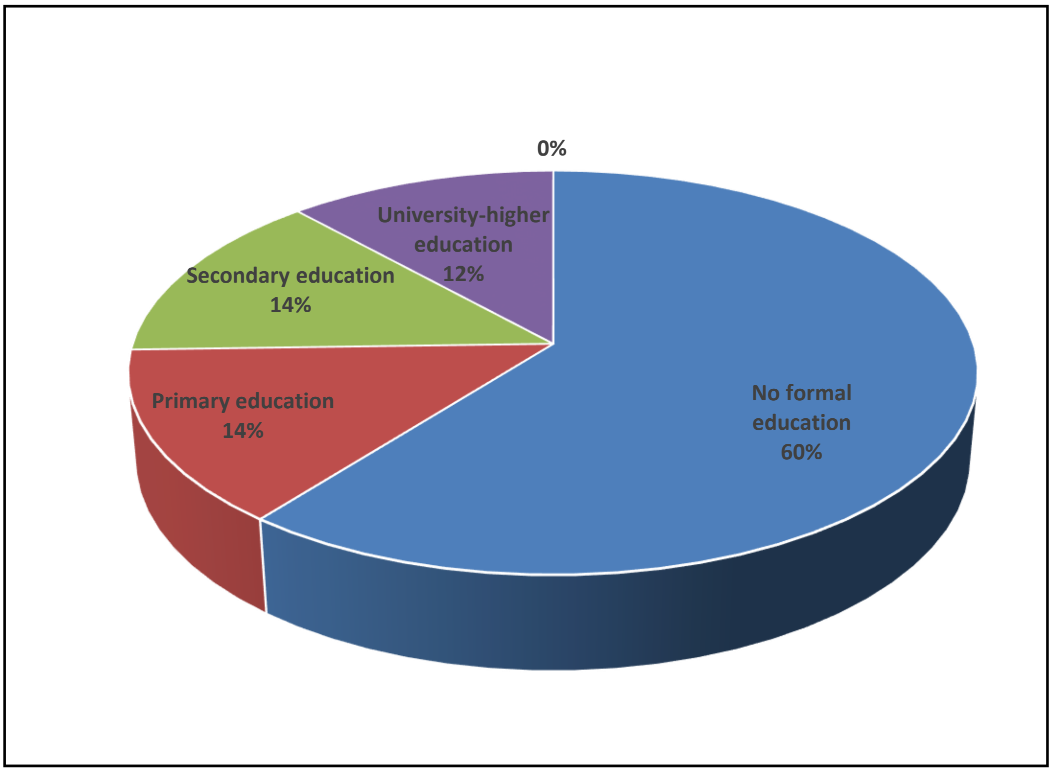


Figure 9. Pilgrims by level of education



2.5.1.2 Xpert MTB/RIF assay results

Xpert MTB/RIF assay results were available for 1,510 (99.9%) of the sputum samples collected (Figure5). Of these 10 (0.66%) nationals and residents from 7 countries were positive for TB. No rifampicin resistance was detected in any of the positive samples; hence by proxy no MDR-TB was detected. The characteristics of pilgrims with positive TB are summarized in Table 5. Most pilgrims originated from India (3, 30%), were male (6, 60%) and had no formal education (5, 50%). Pilgrims positive for TB ranged in age from 49 to 82 years old and six of them had spent from 17 to 35 days in KSA at the time of enrolment in the study. One pilgrim (10%) had traveled to Pakistan in the previous year, five (50%) declared having an underlying health condition but none worked in one of the TB risk occupations in the survey (health care worker, miner, laboratory personnel, refugee camp worker, prison staff). None of the 10 pilgrims were current tobacco (cigarettes, cigars or pipes) smokers but one (10%) had smoked such products in the past. None of the TB positive pilgrims declared coughing blood and only one (10%) reported having been previously treated for TB. The same pilgrim also declared that one of her close contacts was also diagnosed and treated for TB in the past. Three pilgrims (30%) recalled recently (within the previous month) sharing the household with an adult with cough.

Table 5. Characteristics of the tuberculosis positive pilgrims

Pilgrim	Country of residence	Age	Gender	Highest level of education	At risk occupation*	Country travelled 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	Close contacts ever diagnosed or	Rifampicin resistance
1	Afghanistan	60	M	NFE	No	Pakistan	Never	CKD	No	No	Yes	No	No
2	Afghanistan	60	M	NFE	No	None	Never	Hypertension	No	No	Yes	No	No
3	Bangladesh	60	M	NFE	No	None	Never	None	No	No	No	Unsure	No
4	India	82	F	NFE	No	None	Never	Hypertension	No	No	No	No	No
5	India	51	F	PE	No	None	Never	None	No	No	No	No	No
6	India	49	F	PE	No	None	Never	Diabetes	Yes	No	No	Yes	No
7	Indonesia	50	M	HE	No	None	Never	None	No	No	Yes	No	No
8	Pakistan	72	M	PE	No	None	Never	ND	No	No	No	No	No
9	Somalia	59	M	NFE	No	None	Never	None	Unsure	No	Unsure	No	No
10	South Africa	60	F	SE	No	None	Never	Hypertension + Diabetes	No	No	No	No	No

F= Female, M= Male, NFE= No formal education, PE= Primary education, SE= Secondary education, HE= University/higher education, ND= not determine, CKD= Chronic kidney disease

*Health care worker, miner, laboratory personnel, refugee camp worker, prison staff

2.5.1.3 Association between TB and demographic variables

The result of the bivariate analysis showing the association between TB and demographic variables are summarized in Table 6. TB prevalence was statistically significant higher in those with an underlying health condition (p= 0.029), particularly those with chronic kidney disease (p =0.429). Similarly, there was a significant difference in TB prevalence in relation to cough duration (p= 0.0296), with pilgrims coughing between >1-3weeks having the highest prevalence. A near significant association (p= 0.054) was observed in relation to TB treatment.

Although not statistically significant, TB prevalence was also higher in females (1% vs 0.6%), those who traveled outside their country of residency in the previous year (1.2% vs 0.7%), those who had recently lived in a household with an adult with cough (1.9% vs 0.7%) or had close contacts as TB patients (4.2% vs 0.6%), and those taking medications (1.3% vs 0.5%).Pilgrims who declared having been previously treated for TB had higher TB prevalence than those who did not (12.5% vs 0.6%).Similarly, although not statistically significant, prevalence of active TB was lowest among the youngest age group (≤47 year old) and generally increased with age. Also, TB prevalence was highest in those with primary education and those residing in South Asia.

There was a statistically significant increase in risk of TB in relation to having an underlying health condition, previous TB treatment and having a TB patient as a close contact (Table 7). Pilgrims with underlying health conditions were over 4 times more likely to have TB than those who do not have an underlying health condition (OR=4.355; 95% CI= 1.244- 15.249). In particular, pilgrims with chronic kidney disease (OR=38.765; 95% CI= 5.171-290.61; p=0.0004) and hypertension (OR=3.84; 95% CI= 1.03-14.25; p=0.044). Similarly, pilgrims who had previously been treated for TB were 30 times more likely to have TB compared to those not previously treated for TB (OR=30.30; 95% CI= 4.19-219.01; p= 0.0007). Pilgrims with close contacts as TB patients were 9 times more likely to have TB (OR=9.19; 95% CI= 1.49-56.45; p= 0.016).

Although the ORs were not statistically significant, the risk of TB also increased for some other variables (Table 7). For instance, woman were 1.8 times more likely to be TB positive than males. Pilgrims aged >55-64 years old were 2 times more likely to be TB positive than those >64 years old (OR=2.15; 95% CI= 0.47-9.68).

The OR increased 2.8 times in pilgrims with primary education compared to those with no formal education (OR= 2.78; 95% CI= 0.72-10.76). Pilgrims who traveled outside their country of residency in the previous year, those taking medications, and those living in the household with an adult with cough, all were 2.4-3 times more likely to be TB positive. Finally, pilgrims who experienced cough for over 3 weeks were nearly 8 times more likely to be TB positive compared to those who had a cough for less than a week (OR= 7.824; 95% CI= 1.231- 49.71).

Only variables found to be significant at the 2.5% level in the bivariate analysis (Age, underlying health conditions, region lived in for the past year, previous TB treatment, taking medication, cough in household, close contact with TB patient and cough duration) were considered as candidates for 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. Variables that reduced the model performance were removed (close contact with TB patient, previous TB treatment and region lived in for the past year). The results (Table 8) indicate that having and underlying health conditions, taking medication and living in a household with an adult with cough were all significantly associated with TB after adjusting for other factors. Pilgrims with underlying health conditions were nearly 6 times more likely to develop TB (adjusted OR= 5.89; 95% CI= 1.25-27.80). Similarly, those who recently lived in a household with an adult with cough were 4.5 times more likely to have TB (adjusted OR= 4.46; 95% CI= 1.01-19.58). Pilgrims on medications were less likely to be TB positive (adjusted OR= 0.15; 95% CI= 0.02-0.83).

Table 6. Association between tuberculosis and demographic variables

Variable	n	TB+ve	%	p
Gender				0.4795
Female	408	4	1	
Male	1050	6	0.6	
Age				0.1530
≤47	328	0	0	
>47-55	266	3	1.1	
>55-64	384	5	1.3	
>64	373	2	0.5	
Highest level of education				0.5131
No formal education	878	5	0.6	
Primary education	202	3	1.5	
Secondary education	199	1	0.5	
University/ Higher education	170	1	0.6	
Travel outside current reside				0.4410
No	1374	9	0.7	
Yes	82	1	1.2	
Region lived in for the past year				0.2544
South Asia	734	8	1.1	
Former Soviets	213	0	0	
Other African Countries	355	2	0.6	
North Africa	205	0	0	
Underlying health conditions				**0.0293**
No	1124	4	0.4	
Yes	319	5	1.6	
Chronic kidney disease				**0.0429**
No	1436	8	0.6	
Yes	7	1	14.3	
Chronic liver disease				1.0000
No	1440	9	0.6	
Yes	3	0	0	
Chronic lung disease				1.0000
No	1426	9	0.6	
Yes	17	0	0	

Cont.…Table 6. Association between tuberculosis and demographic variables

Variable	N	TB+ve	%	p
Cardiovascular disease				1.0000
No	1423	9	0.6	
Yes	20	0	0	
Hypertension				0.0896
No	1264	6	0.5	
Yes	179	3	1.7	
Diabetes				0.2052
No	1307	7	0.5	
Yes	136	2	1.5	
Not Listed				1.0000
No	1368	9	0.7	
Yes	75	0	0	
Smoking				1.0000
No	1370	10	0.7	
Yes	110	0	0	
Past smoking				1.0000
No	1231	9	0.7	
Yes	126	0	0	
Previous TB treatment				0.0541
No	1295	8	0.6	
Yes	8	1	12.5	
Cough in household				0.1545
No	867	6	0.7	
Yes	161	3	1.9	
Close contacts TB patient				0.1599
No	1232	8	0.6	
Yes	24	1	4.2	
Any medication				0.2404
No	1136	6	0.5	
Yes	320	4	1.3	
Cough up blood				1.0000
No	1375	9	0.7	
Yes	30	0	0	

Cont... Table 6. Association between tuberculosis and demographic variables

Variable	N	TB+ve	%	p
Pregnancy				0.7205
Not Applicable	1055	6	0.6	
No	417	3	0.7	
Yes	1	0	0	
Current or Past smoker				0.3778
No	1270	10	0.8	
Yes	236	0	0	
Cough length (Days)				**0.0296**
<= 1 Week	1195	5	0.4	
>1 to 2 Weeks	84	2	2.4	
>2 to 3 Weeks	42	1	2.4	
> 3 Weeks	74	1	1.4	

Table 7. Demographic variables and risk of tuberculosis

Variable	n	TB +ve	%	OR (95% CI)	p
Gender					
Female	408	4	1	1	
Male	1050	6	0.6	0.559(0.167,1.873)	0.3461
Age					
>64	373	2	0.5	1	
≤47	328	0	0	0.226 (0.011,4.749)	0.1750
>47-55	266	3	1.1	1.974 (0.385,10.107)	0.2269
>55-64	384	5	1.3	2.154 (0.479,9.689)	0.1370
Highest level of education					
No formal education	878	5	0.6	1	
Primary education	202	3	1.5	2.786 (0.721,10.762)	0.2112
Secondary education	199	1	0.5	1.2 (0.195,7.376)	0.7610
University/ Higher education	170	1	0.6	1.405 (0.228,8.651)	0.9449
Travel outside current reside					
No	1374	9	0.7	1	
Yes	82	1	1.2	2.645 (0.462,15.158)	0.2747
Region lived in for the past year					
South Asia	734	8	1.1	1	
Former Soviets	213	0	0	0.2 (0.011,3.505)	0.5449
Other African Countries	355	2	0.6	0.208 (0.012,3.642)	0.5497
North Africa	205	0	0	0.604 (0.146,2.495)	0.5675
Underlying health conditions					
Cardiovascular disease					
No	1423	9	0.6	1	
Yes	20	0	0	3.632 (0.191,69.016)	0.3906
Hypertension					

Cont.. Table 7. Demographic variables and risk of tuberculosis

Variable	N	TB +ve	%	OR (95% CI)	p
No	1124	4	0.4	1	
Yes	319	5	1.6	4.355 (1.244,15.249)	**0.0214**
Chronic kidney disease					
No	1436	8	0.6	1	
Yes	7	1	14.3	38.765 (5.171,290.62)	**0.0004**
Chronic liver disease					
No	1440	9	0.6	1	
Yes	3	0	0	21.514 (0.662,699.27)	0.0841
Chronic lung disease					
No	1426	9	0.6	1	
Yes	17	0	0	4.264 (0.22,82.449)	0.3373
No	1264	6	0.5	1	
Yes	179	3	1.7	3.84 (1.035,14.252)	**0.0444**
Diabetes					
No	1307	7	0.5	1	
Yes	136	2	1.5	3.223 (0.759,13.691)	0.1128
Not Listed					
No	1368	9	0.7	1	
Yes	75	0	0	0.948(0.054,16.733)	0.9711
Smoking					
No	1370	10	0.7	1	
Yes	110	0	0	0.586 (0.034,10.197)	0.7140
Past smoking					
No	1231	9	0.7	1	
Yes	126	0	0	0.509 (0.029,8.886)	0.6432
Previous TB treatment					
No	1295	8	0.6	1	
Yes	8	1	12.5	30.306 (4.193,219.014)	**0.0007**
Cough in household					
No	867	6	0.7	1	
Yes	161	3	1.9	2.927 (0.787,10.883)	0.1090
Close contacts TB patient					
No	1232	8	0.6	1	
Yes	24	1	4.2	9.196 (1.498,56.456)	**0.0166**
Any medication					
No	1136	6	0.5	1	
Yes	320	4	1.3	2.473 (0.738,8.292)	0.1423
Cough up blood					
No	1375	9	0.7	1	
Yes	30	0	0	2.36 (0.128,43.339)	0.5631

Cont.…Table 7. Demographic variables and risk of tuberculosis

Variable	N	TB +ve	%	OR (95% CI)	p
Pregnancy					
Not Applicable	1055	6	0.6	1	
No	417	3	0.7	1.363 (0.369,5.031)	0.1946
Yes	1	0	0	53.107(0.53,5318.358)	0.1030
Current or Past smoker					
No	1270	10	0.8	1	
Yes	236	0	0	0.254 (0.015,4.371)	0.3450
Cough length (Days)					
<= 1 Week	1195	5	0.4	1	
>1 to 2 Weeks	84	2	2.4	4.417 (0.708,27.552)	0.3632
>2 to 3 Weeks	42	1	2.4	6.559 (1.437,29.929)	0.3106
> 3 Weeks	74	1	1.4	7.824 (1.231,49.71)	0.8495

Table 8. Results of the multivariate analysis

Variable	aOR (95% CI)	p
Age		
≤47	1	
>47-55	5.781 (0.382,87.399)	0.5014
>55-64	9.488 (0.651,138.237)	0.1067
>64	4.195 (0.247,71.381)	0.9090
Underlying health conditions		
No	1	
Yes	5.899 (1.252,27.804)	0.0249
Cough in household		
No	1	
Yes	4.466 (1.019,19.581)	0.0472
Any medication		
No	1	
Yes	0.152 (0.028,0.834)	0.0301
Cough length (Days)		
<= 1 Week	1	
>1 to 2 Weeks	1.842 (0.247,13.745)	0.7621
>2 to 3 Weeks	3.876 (0.479,31.371)	0.4510
> 3 Weeks	3.784 (0.576,24.862)	0.4399

aOR=adjusted odd ratio

2.5.2 Tuberculosis among hospitalised pilgrims

The study enrolled 347 pilgrims symptomatic for cough of any duration that were admitted during the study period at the selected healthcare facilities. Of these 43 (12.4%) produced saliva samples and hence were excluded from the study (Figure10). The remaining 304 patients were able to produce sputum samples, and these were tested using the MTB/RIF assay. All these patients had valid sputum sample results and were included in the analysis.

2.5.2.1 Characteristics of the study population

The characteristics of the study population are summarized and presented in Tables 9-11 and Figures11-18. Patients were nationals of 44 countries in Africa, Asia, Europe and the United States of America (USA) (Table 9). Most of these patients resided in South Asia (29.9%) and North Africa (20.4%). Countries of residence most represented among the study population were Indonesia (36, 11.8%), India (35, 11.5%), Egypt (28, 9.2%) and Bangladesh (26, 8.6%).

The mean age of the study population was 61.6 (SD= 12.9 years, range= 21-99 years) with a male: female ratio of 2:1. Nearly 47% of the patients had no formal education and 65% had underlying health conditions. Hypertension and diabetes, chronic lung disease and cardiovascular disease were the most common co-morbidities represent respectively in 33%, 24%, 22.6% and 18% of those with underlying health conditions (Table 10). Similarly, 60% reported that they were taking medications at the time of the study. One pilgrim from Ghana was pregnant at the time of enrolment in the study.

Nearly 34% of the patients declared that they were smokers of tobacco products such as cigarettes, cigars or pipes or have smoked such products in the past. At the time of enrolment, 19.5% of patients were current smokers (Table 9). A small minority (2.2%) of the patients had occupations associated with increased risk of TB infection (Table 9). Travel information indicated that 39 (13.4%) patients had traveled outside their country of residence in the previous year visiting countries in Africa, Asia, the Middle East and Europe. The most common destination visited was KSA (42.5%). The purpose of visiting KSA in the previous year was probably to perform Umrah/Hajj, as nearly all patients (14/17, 82.3%) who reported visiting KSA also reported performing Umrah/Hajj in the previous year. In general, 7.2% (21/293) of the patients reported performing Hajj or Umrah in the previous year.

At the time of recruitment, most patients (85.2%) reported a cough of 2 week or less in duration. Twenty-four patients (9.7%) declared that they were coughing blood and 33 (12.8%) stated that within the previous month they shared the household with an adult with a cough (Table 9). A minority of pilgrims (1.9%) stated that they have had a close contact diagnosed or treated for TB. Three patients declared that they were receiving TB treatment at the time of enrolment.

Twelve patients (4.4%) declared that they had been previously treated for TB and 5 confirmed that they had completed their TB treatment. Of these 5, four reported treatment duration of 6-12 months while one reported being treated for 2-5 months. In general, the reported TB treatment duration was below 6 months in 41.7% of those reporting previous TB treatment (Table 9). Half of those previously treated for TB originated from Indonesia.

2.5.2.2 Clinical data of the study population

Most patients were admitted to emergency rooms (89/295, 30.2%) and isolation wards (28.1%) followed by general wards (26.8%). Upon admission, 392 initial diagnoses according to the International Classification of Diseases (ICD)-10 were documented in 262 patients (Table 11). These were mainly diseases of the respiratory system (252, 64.3%) followed by diseases of the circulatory system (35, 8.9%). Pneumonia was the most common admission diagnosis reported in 41.6% (109/262) of the cases. MERS-CoV and influenza H1N1 was suspected in respectively 21.7% (57/262) and 7.2% (19/262) of the cases.

TB was tested in 26 (9.4%) patients, mainly using sputum AFB (23, 88.5%) and chest X-ray (8, 30.8%), but none were tested using GeneXpert MTR/RIF. Of those with TB test results, 5 (29.4%) cases were positive for TB and in these patients, TB was the final diagnosis. One case had a TB result of MDR-TB however, final diagnosis was not reported as TB. Hence, TB was reported as final diagnosis in 2.2% (5/225) of the cases (2.2%). Of these, one was discharged, one died, one was still an inpatient in the same hospital by the end of the study period, and 2 were referred to other healthcare facilities for treatment. In general, data on final diagnosis was available for 224 cases for whom 300 final diagnoses as per the ICD-10 chapters were made (Table 11). Most were diseases of the respiratory system (201, 67%) followed by diseases of the circulatory system (29, 9.7%).

Pneumonia was the most common final diagnosis reported in 48.6% (109/224) of the cases. Influenza H1N1 was identified in 12% (27/224) of the cases and no cases of MERS were reported.

Data on the outcome of the cases by the end of the study period was available for 236 cases (Table 11). Of these, most (83.9%) were discharged, 13.2% were inpatients, within the same healthcare facility or after being referred to other institutions. Mortality was recorded in 6 (2.5%) cases.

Figure 10. Flow chart of the hospitalised pilgrims study enrolment and results (By author)

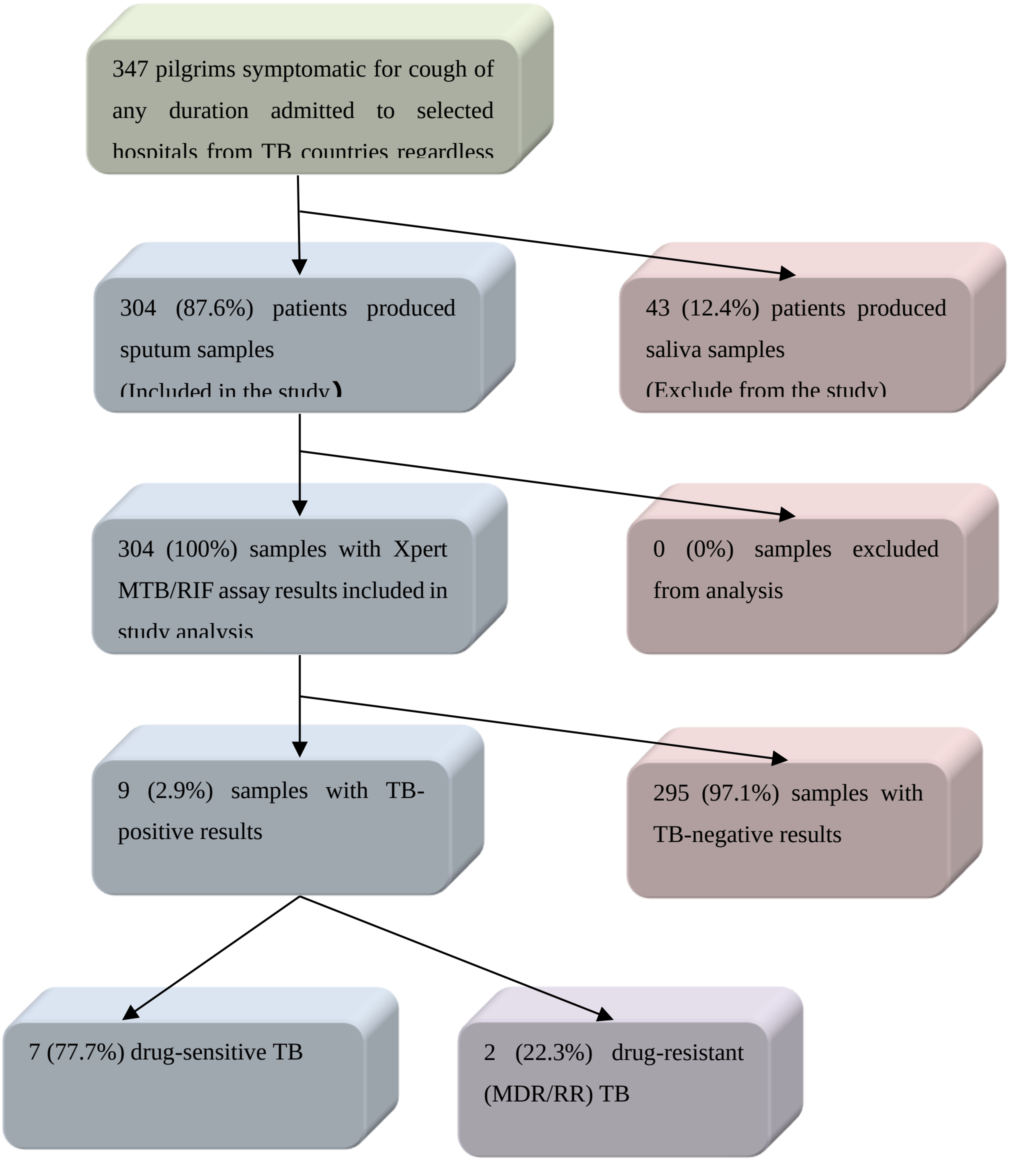


Table 9. Characteristics of the enrolled patients' population

Variable	Number (n)	Percentage (%)
Patients enrolled	**304**	
Gender	**302**	
Male	202	66.9
Female	100	33.1
Age	**297**	
Mean (Range)	**61.63 (21-99)**	
<53	74	24.9
53 – 63	85	28.6
64 – 70	65	21.9
>70	73	24.6
Nationality	**304**	
Afghanistan	4	1.3
Algeria	8	2.6
Bangladesh	26	8.6
Burkina Faso	2	.7
Cameroon	1	.3
Chad	1	.3
China	3	1.0
Comoros	1	.3
Egypt	28	9.2
Ethiopia	8	2.6
France	2	.7
Ghana	2	.7
Greece	1	.3
Guinea	1	.3
India	36	11.5
Indonesia	36	11.8
Iran	3	1.0
Iraq	6	2.0
Ivory Coast	1	.3
Jordan	1	.3
Lebanon	2	.7
Libya	3	1.0
Malaysia	7	2.3

Cont... **Table 9. Characteristics of the enrolled patients' population**

Variable	Number (n)	Percentage (%)
Mali	1	.3
Morocco	15	4.9
Myanmar	1	.3
Nepal	3	1.0
Niger	5	1.6
Nigeria	10	3.3
Pakistan	20	6.6
Palestine	7	2.3
Philippines	4	1.3
Saudi Arabia	6	2.0
Somalia	7	2.3
Spain	1	.3
Sudan	8	2.6
Switzerland	1	.3
Syria	8	2.6
Thailand	1	.3
Tunisia	5	1.6
Turkey	4	1.3
United Kingdom	1	.3
United States	2	.7
Yemen	11	3.6
Country of residence in the past year	**304**	
Afghanistan	4	1.3
Algeria	8	2.6
Bangladesh	26	8.6
Burkina Faso	2	.7
Cameroon	1	.3
Chad	1	.3
China	3	1.0
Comoros	1	.3
Egypt	28	9.2
Ethiopia	8	2.6
France	3	1.0
Germany	1	.3

Cont.…**Table 9. Characteristics of the enrolled patients' population**

Variable	**Number (n)**	**Percentage (%)**
Ghana	2	.7
Greece	1	.3
Guinea	1	.3
India	35	11.5
Indonesia	36	11.8
Iran	3	1.0
Iraq	6	2.0
Italy	1	.3
Ivory Coast	1	.3
Jordan	3	1.0
Lebanon	3	1.0
Libya	3	1.0
Malaysia	7	2.3
Mali	1	.3
Morocco	13	4.3
Myanmar	1	.3
Nepal	3	1.0
Niger	5	1.6
Nigeria	10	3.3
Pakistan	20	6.6
Palestine	6	2.0
Philippines	3	1.0
Saudi Arabia	11	3.6
Somalia	7	2.3
Sudan	7	2.3
Syria	5	1.6
Thailand	1	.3
Tunisia	4	1.3
Turkey	5	1.6
United Kingdom	2	.7

Cont.…**Table 9. Characteristics of the enrolled patients' population**

Variable	Number (n)	Percentage (%)
United States	3	1.0
Yemen	9	3.0
Region lived in in the past year	**304**	
East Asia	51	16.8
Europe & US	11	3.6
North Africa	62	20.4
Other African Countries	41	13.4
South Asia	91	29.9
West Asia	48	15.8
Level of education	**290**	
No formal education	134	46.2
Primary education	56	19.3
Secondary education	63	21.7
University-higher education	37	12.8
Occupation	**284**	
Health care worker	4	1.4
Miner	1	0.4
Laboratory personnel	1	0.4
Refugee camp worker	0	0.0
Prison staff	0	0.0
None of the above	278	97.9
Pregnancy	**299**	
Yes	1	0.3
No	83	27.8
NA	215	71.9
Underlying health conditions	**288**	
Yes	187	64.9
No	101	35.1
Chronic kidney disease	**288**	
No	280	97.2
Yes	8	2.8
Chronic liver disease	**288**	
No	283	98.3
Yes	5	1.7

Cont.…**Table 9. Characteristics of the enrolled patients' population**

Variable	Number (n)	Percentage (%)
Chronic lung disease	**288**	
No	223	77.4
Yes	65	22.6
Cardiovascular disease	**288**	
No	236	81.9
Yes	52	18.1
Hypertension	**288**	
No	193	67.0
Yes	95	33.0
Cancer	**288**	
No	287	99.7
Yes	1	0.3
Immunosuppressive illness	**288**	
No	288	100
Yes	0	0.00
Diabetes	**288**	
No	219	76.0
Yes	69	24.0
Stroke	**288**	
No	286	99.3
Yes	2	0.7
Not Listed	**288**	
No	269	93.4
Yes	19	6.6
Travel outside current country of residence in the past year	**290**	
Yes	39	13.4
No	251	86.6
Hajj/Umrah (Past-year)	**293**	
No	266	90.8
Yes	21	7.2
Don't recall	6	2.0
Smoking (Current)	**292**	
No	235	80.5
Yes	57	19.5

Cont.…**Table 9. Characteristics of the enrolled patients' population**

Variable	Number (n)	Percentage (%)
Past smoking	**223**	
No	187	83.9
Yes	36	16.1
Any medication	**285**	
No	171	60.0
Yes	114	40.0
Previous TB treatment	**272**	
No	236	86.8
Yes	12	4.4
Don't know	24	8.8
TB treatment duration	**12**	
1 month	2	16.7
2-5 months	3	25.0
6-12 months	5	41.0
12 months	0	0.0
Don't recall	2	16.7
TB treatment completed	**10**	
Yes	5	50.0
No	5	50.0
Current TB treatment	**11**	
No	8	72.7
Yes	3	27.3
Cough in household	**256**	
No	219	85.5
Yes	33	12.9
Don't know	4	1.6
Close contacts TB patient	**257**	
No	219	85.2
Yes	5	1.90
Don't know	33	12.8
Cough up blood	**248**	
No	224	90.3
Yes	24	9.7

Cont.…**Table 9. Characteristics of the enrolled patients' population**

Variable	**Number (n)**	**Percentage (%)**
Cough length (Days)	**263**	
<= 1 Week	164	62.4
>1 to 2 Weeks	60	22.8
>2 to 3 Weeks	14	5.3
> 3 Weeks	25	9.5

TB=Tuberculosis, US=United States of America, NA= not applicable

Table 10. Underlying health conditions among enrolled patients

Underlying health conditions	**n= 288**	**Percentage (%)**
Hypertension	95	33
Diabetes	69	24
Chronic kidney disease	8	2.8
Chronic lung disease	65	22.6
Chronic liver disease	5	1.7
Cardiovascular disease	52	18
Stroke	2	0.7
Cancer	1	0.3
Immunosuppressive illness	0	0.0
Other	19	6.6

Table 11. Clinical data of the enrolled patients

Variable	Number (n)	Percentage (%)
Admission ward	**295**	
Other	13	4.4
ER	89	30.2
ICU	21	7.1
General ward	79	26.8
Isolation ward	83	28.1
Surgical ward	10	3.4
Duration of current illness	**261**	
<1 week	195	74.7
1 -2 weeks	56	21.5
3 - 4 weeks	5	1.9
>4 weeks	5	1.9
Patient tested for TB	**278**	
No	231	83.1
Yes	26	9.4
NA	21	7.6
TB tests performed	**26**	
Sputum AFB	23	88.5
Chest X-ray	8	30.8
GeneXpert MTR/RIF	0	0
Sputum culture	6	23.1
TB test positive	**17**	
No	12	70.6
Yes	5	29.4
MDRT-positive results	**5**	
No	4	80.0
Yes	1	20.0
Admission diagnosis by ICD-10 chapters	**392**	
Diseases of the respiratory system	252	64.3
Diseases of the circulatory system	35	8.9
Certain infectious and parasitic diseases	28	7.1
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	28	7.1
Injury, poisoning and certain other consequences of external causes	16	4.1
Other <4%	33	8.4

Cont..**Table 11. Clinical data of the enrolled patients**

Variable	Number (n)	Percentage (%)
Final diagnosis by ICD-10 chapters	**300**	
Diseases of the respiratory system	201	67.0
Diseases of the circulatory system	29	9.7
Certain infectious and parasitic diseases	15	5.0
Injury, poisoning and certain other consequences of external causes	12	4.0
Other <4%	43	14.3
Case outcome	**236**	
Still at the hospital	24	10.2
Discharged	198	83.9
Deceased	6	2.5
Defaulted	1	.4
Referred	7	3.0

TB=tuberculosis, NA=not applicable, ICU=intensive care unit, ER=emergency room, AFB=acid fast bacilli, ICD=international classification of diseases

Figure 11. Patients by age

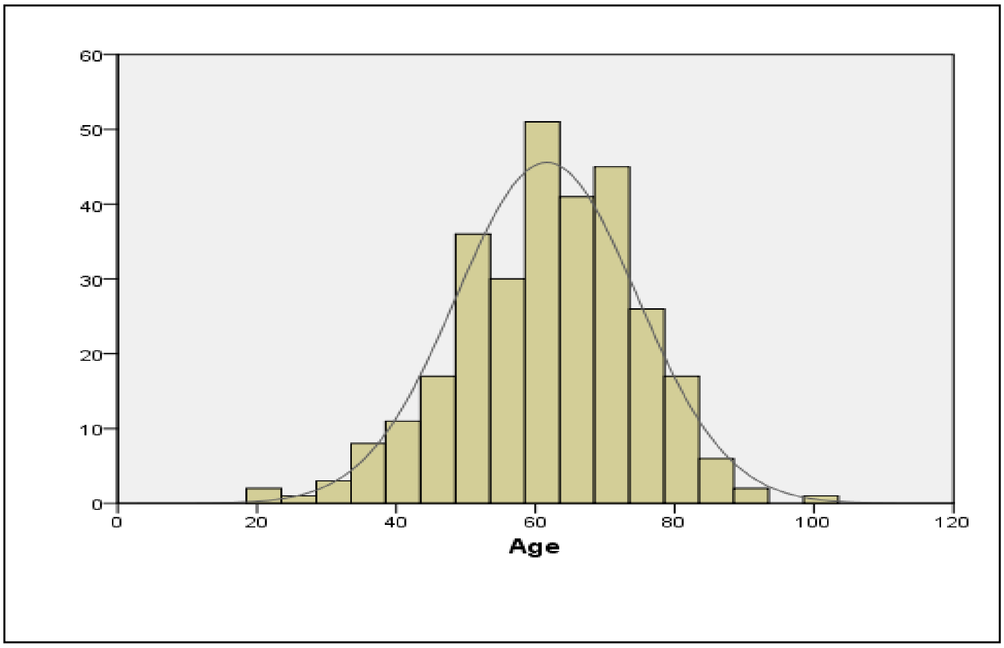


Figure 12. Patients by age group

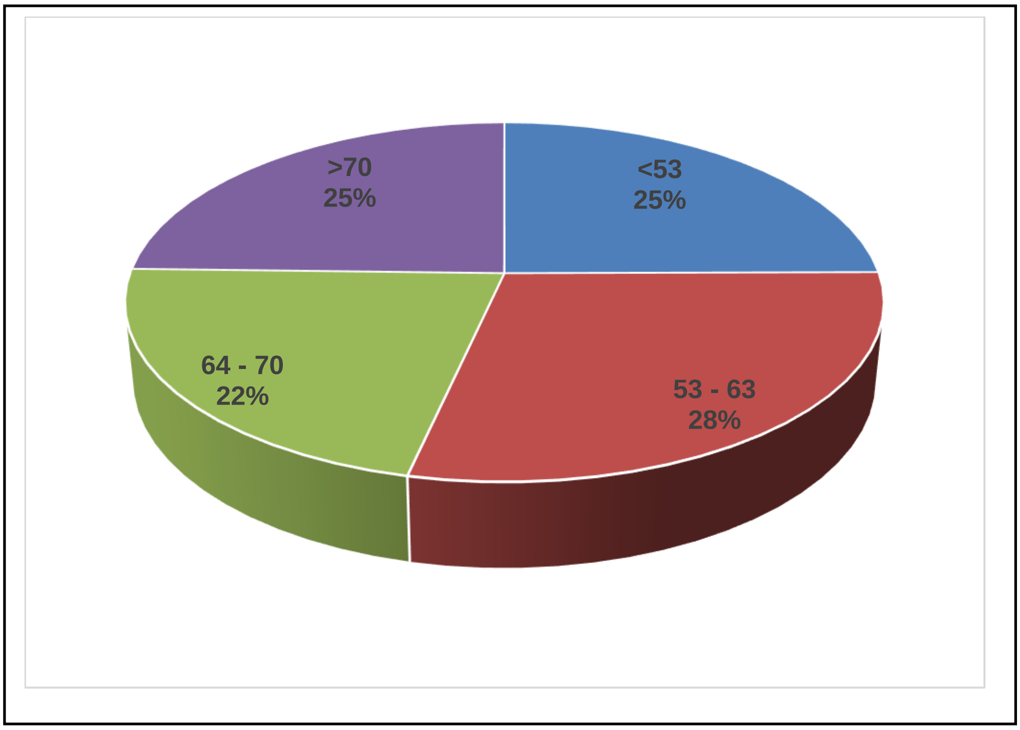


Figure 13. Patients by residency region

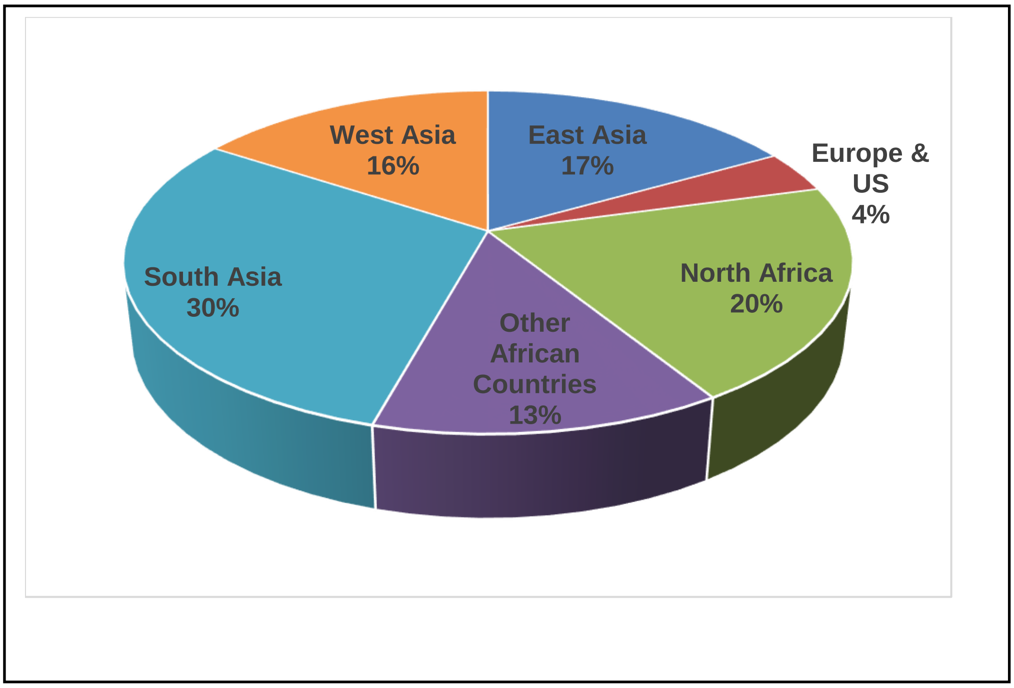


Figure 14. Patients by level of education

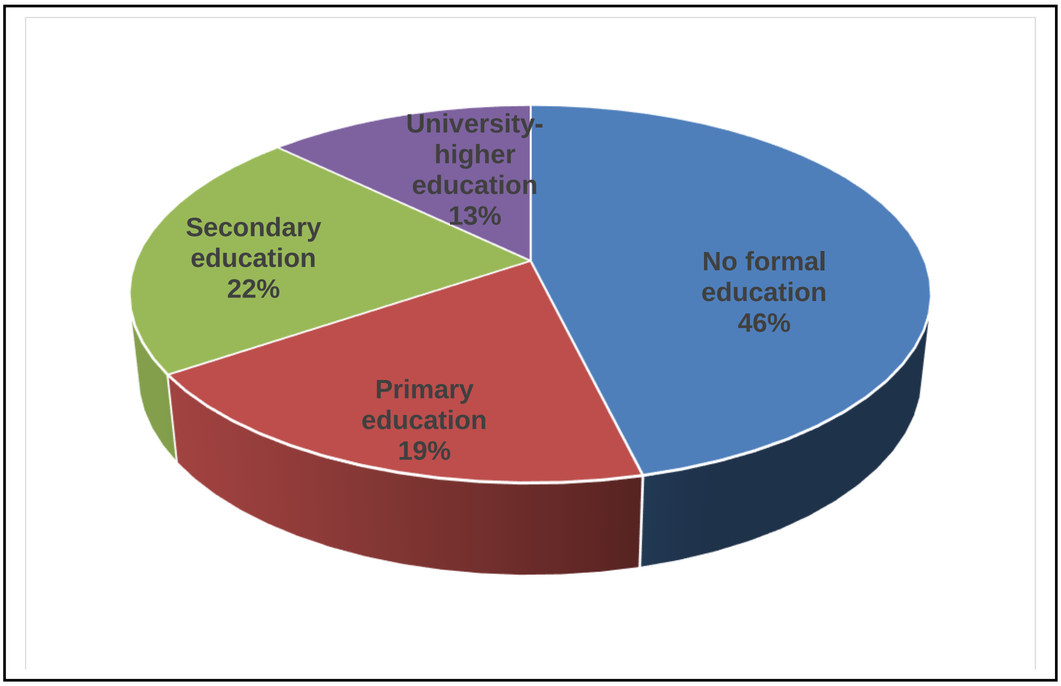


Figure 15. Patients by admission ward

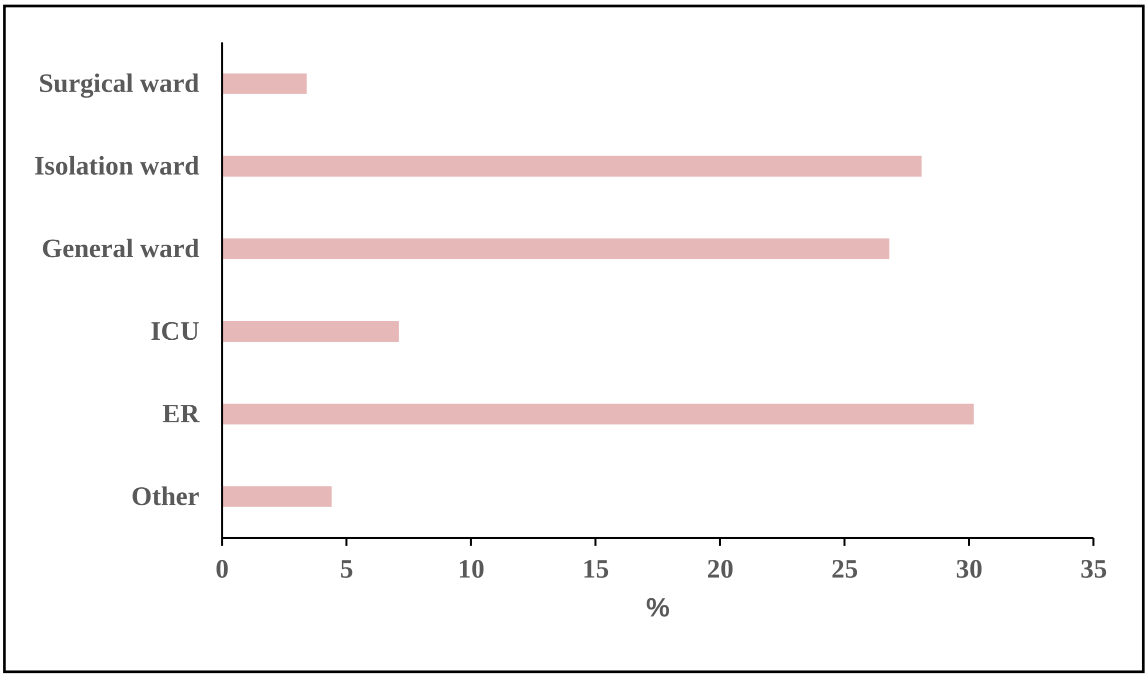


Figure 16. Patients by admission diagnosis (ICD-10 chapters)

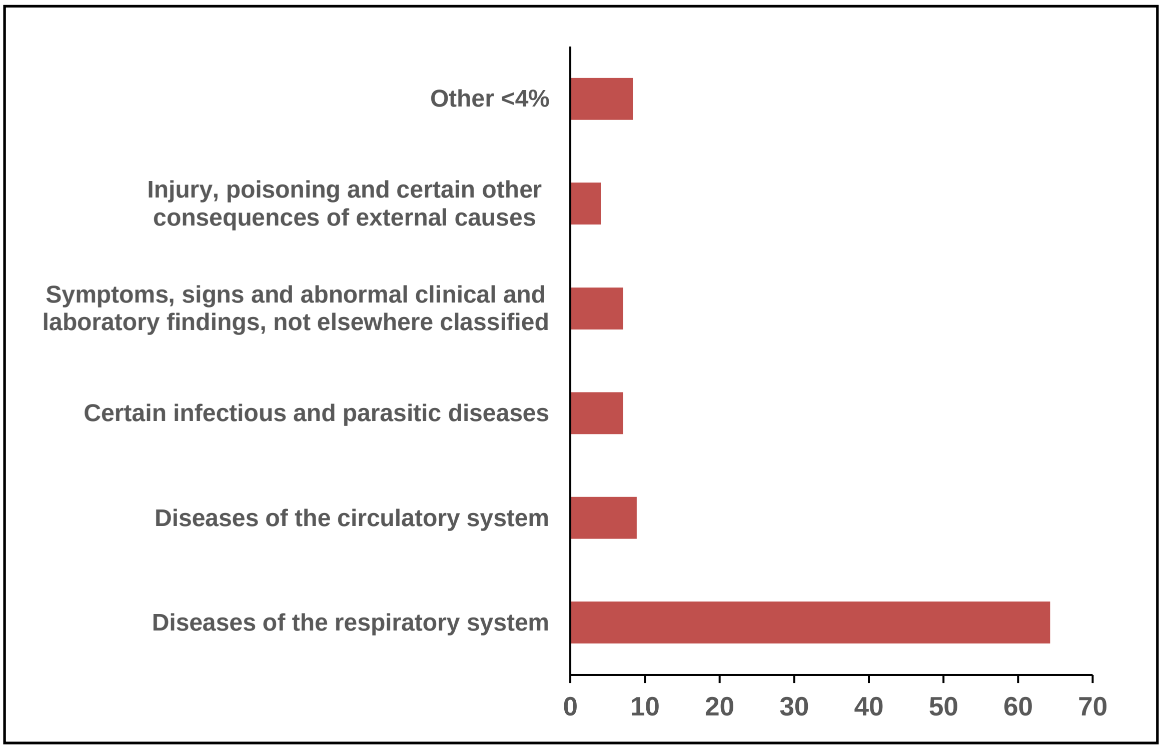


Figure 17. Patients by final diagnosis (ICD-10 chapters)

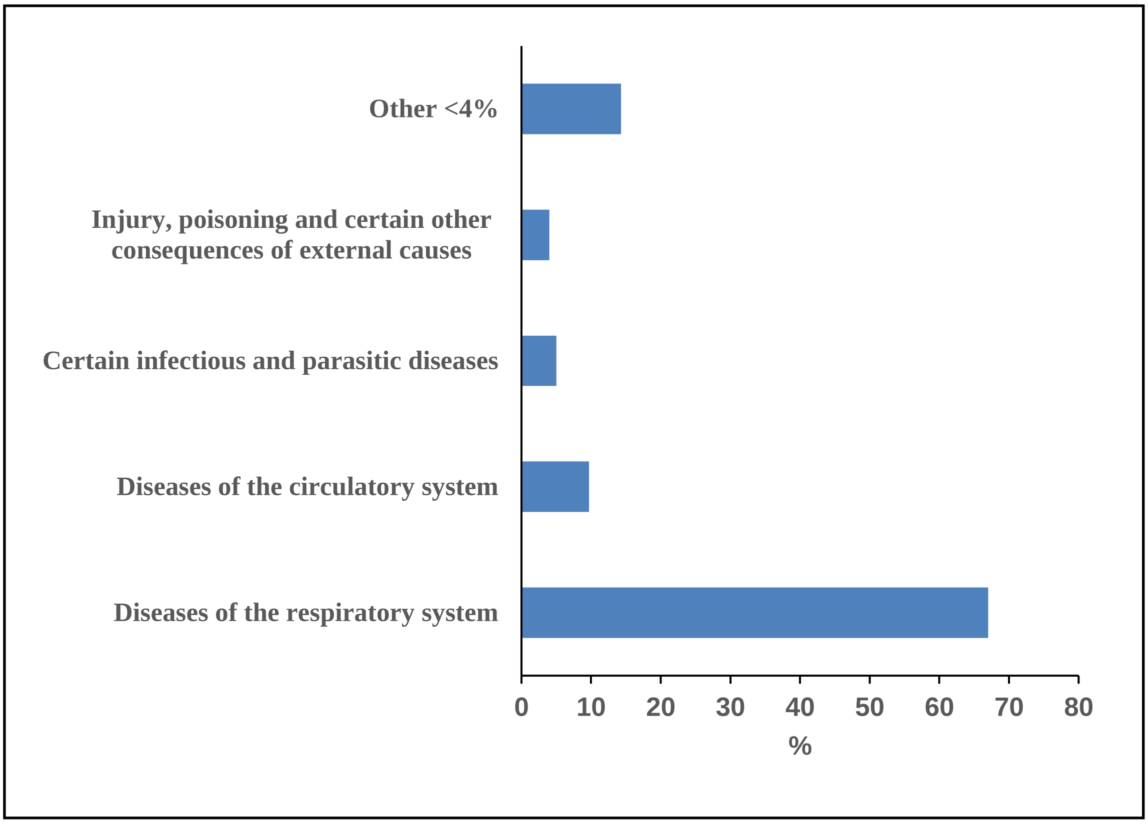
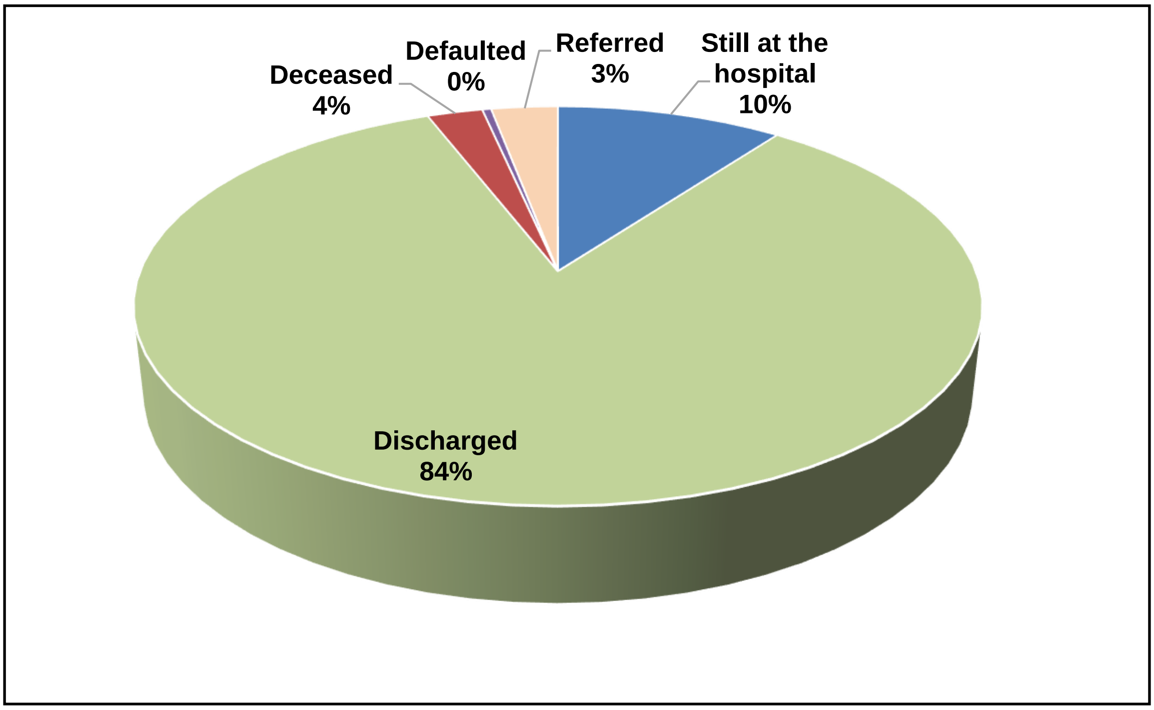


Figure 18. Patients by case outcome



2.5.2.3 Xpert MTB/RIF assay results

Xpert MTB/RIF assay results were available for all of the 304 sputum samples collected (Figure10). Of these 9 (2.9%) nationals and residents from 6 countries were positive for TB. Rifampicin resistance was detected in two samples, hence possible MDR-TB was detected in these two (22.2%) cases. The latter cases originated from India and Indonesia. The characteristics of pilgrims with positive TB are summarized in Table 12. Most pilgrims originated from Indonesia (3, 33.3%) and India (2, 22.2%), were male (6, 66.6%) and had no formal education (5, 55.5%). Pilgrims positive for TB ranged in age from 37 to 78 years old. Data on arrival date to KSA was available for 3 of the drug-sensitive TB cases and indicated that these pilgrims spent 12 to 31 days in KSA before hospital admission. One (11.1%) pilgrim with rifampicin-resistant TB indicated traveling outside her country of residency in the previous year, visiting Malaysia.

Five (55.5%) pilgrims declared having an underlying health condition but none worked in one of the TB risk occupations in the survey (health care worker, miner, laboratory personnel, refugee camp worker, prison staff). One (11.1%) pilgrim declared being a current tobacco (cigarettes, cigars or pipes) smoker and two (22.2%) had smoked such products in the past. None of the TB positive pilgrims declared coughing blood and only two (22.2%) reported having been previously treated for TB. Of the latter, one drug-sensitive TB case declared having been treated for TB for ≤ 1 month and having not finished their TB treatment. The other case, a rifampicin-resistant TB case, declared having been treated for TB in the past for a duration of 6-12 months and having completed their TB treatment. None of the TB positive pilgrims declared that they had close contacts diagnosed or treated for TB in the past, but one (11.1%) recalled recently (within the previous month) sharing the household with an adult with cough.

On hospital admission, most TB cases (6, 66.6%), including the two MDR-TB cases, were admitted to an isolation ward. Two other cases were admitted to ER and one to a surgical ward. Admission diagnosis was available for 7 out of the 9 TB cases, all of whom had diseases of the respiratory system, specifically pneumonia (6, 85.7%). In addition to pneumonia, one case also had an admission diagnosis of suspected TB. Three of the TB cases were tested for TB in hospital: one using chest X-ray and sputum culture and another using chest X-ray and sputum AFB. Both cases were diagnosed with TB and were started on anti-TB medication.

Although one of these two cases were detected in the study as a MDR-TB case, there was no indication that the hospital did diagnose the case as a MDR-TB case. The last case tested in hospital for TB was tested using sputum AFB only. Although the case was also identified in the current study as a MDR-TB, no information on the final diagnosis of the case or treatment were available, hence it is not possible to determine if the hospital did identify the case as TB or MDR-TB. Final diagnosis was available for 6 out of the 9 TB cases, two of whom were diagnosed with TB (as highlighted above) and the majority of the rest (3/4, 75%) were diagnosed with pneumonia. This means that the prevalence of missed active TB among the study populations was 2.3% (7/304).

Most cases (5, 55.5%) were discharged from healthcare facilities, three cases (33.3%) were still inpatients at the end of the study period, one of whom was referred to another healthcare facility for further treatment. As the final diagnosis of one of the MDR-TB detected by this study was not documented, and the MDR status of the other MDRT-TB case identified in the study was not available, this means that out of the 9 TB cases identified only 2-3 (22.2-33.3%) were diagnose by the hospital as TB cases. This means that 66.7-77.8% of the TB cases identified in the study were missed by the hospital. Also, potentially none of the MDR-TB cases identified in this study were actually diagnosed as MDR-TB by the hospitals.

Results also show that while 5 cases of TB were diagnosed by the healthcare facilities among the study population using chest X-ray, sputum culture and/or sputum AFB tests, only 2 (40%) of these were positive in the Xpert MTB/RIF assay. Samples from 3 TB confirmed cases by the healthcare facilities were negative in the Xpert MTB/RIF assay.

Table 12. Characteristics of the tuberculosis positive patients

Pilgrim	Country of residence	Age	Gender	Highest level of education	At risk occupation*	Country travelled to in the last year	Tobacco smoker	Underlying health condition(s)	Previously treated for TB	Currently coughing up blood	Recently lived in a household with an adult with a cough	Close contacts ever diagnosed or treated for TB	Rifampicin resistance	Case detected by the hospital	Case outcome
1	India	65	M	NFE	No	None	Never	None	No	No	No	No	No	No	ND
2	India	78	M	NFE	ND	None	Never	None	Unsure	No	ND	ND	Yes	No	DI
3	Indonesia	37	F	HE	No	Malaysia	Never	Diabetes	Yes	No	No	No	Yes	Yes₸	RF
4	Indonesia	74	M	SE	No	None	Past	Hypertension Diabetes	No	No	No	No	No	No	DI
5	Indonesia	41	M	HE	No	None	Current	None	No	No	No	No	No	No	DI
6	Nepal	50	M	NFE	No	None	Never	None	No	No	Yes	No	No	No	DI
7	Pakistan	65	F	NFE	No	None	Never	Hypertension	Unsure	No	No	Unsure	No	No	IP
8	Philippines	ND	F	NFE	No	None	Past	Diabetes	Yes	No	No	No	No	Yes	IP
9	Sudan	45	M	PE	No	None	Never	CLD	No	No	No	No	No	No	DI

F= Female, M, Male, NFE= No formal education, PE= Primary education, SE= Secondary education, HE= University/higher education, ND= not determine, CLD= Chronic lung disease; IP= Inpatient, RF= Referred, DI= Discharged

*Health care worker, miner, laboratory personnel, refugee camp worker, prison staff

₸Detected by the hospital as a TB case but not as MDR-TB case.

2.5.2.4 Association between tuberculosis and demographic and clinical variables

The result of the bivariate analysis showing the association between TB and demographic and clinical variables are summarized in Table 13. TB prevalence was statistically significantly higher in those who had previously been treated for TB (p= 0.015). A near significant difference (p= 0.062) was observed in relation to hospital admission wards, with patients admitted to surgical and isolation wards having the highest TB prevalence.

Although not statistically significant, TB prevalence was also higher among those residing in East Asia (7.8%), among smokers (3.2% vs 2.7%), those symptomatic for cough of over a week (4% vs 2.4%). Also, TB prevalence was highest in those under 53 years old, those with university of higher education, those with no underlying health conditions and those not on medication (Table 13).

There was a statistically significant increase in risk of TB in relation to ward of admission and previous TB treatment (Table 14). Patients admitted to an isolation ward were over 5 times more likely to be TB positive than those admitted to other wards (OR= 5.429; 95% CI= 1.325- 22.242, p=0.019). Similarly, patient who had a history of TB treatment were over 9 times more likely to have TB (OR= 9.240; 95% CI= 1.593-53.588, p=0.013).

Although the ORs were not statistically significant, the risk of TB also increased for some other variables (Table 14). For instance, patients with no formal education were 1.4 times (OR= 1.473; 95% CI= 0.387-5.6) more likely to be TB positive compared to those with some form of education (primary, secondary of higher education). There was around 1.3 times increase in risk of TB for patients who declared being current or past smokers (OR= 1.213; 95% CI= 0.284-5.191) and those coughing up blood (OR= 1.348; 95% CI= 0.159-11.443). Patients who had a cough for >2-3 weeks were 3 times more likely to be TB positive compared to those with a cough lasting less than a week (OR= 3.077; 95% CI= 0.320-29.576). Also, patients residing in Asia had much higher risk of TB than those residing in Europe & US or Africa.

Only variables found to be significant at the 2.5% level in the bivariate analysis (previous TB treatment and admission ward) were considered as candidates for 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 the current study with such a small number of events. The results (Table 15) indicate that previous TB treatment was an independent factor associated with TB. Patient who had history of TB treatment were 8 times more likely to be TB positive after adjusting for other factors (adjusted OR [aOR]= 8.1; 95% CI= 1.351-48.464, p= 0.022).

Table 13. Association between tuberculosis and demographic variables

Variable	n	TB+ve	%	p
Gender				
Male	100	3	3.0	1.000
Female	202	6	3.0	
Age				0.149
Mean (Range)				
<53	74	4	5.4	
53 – 63	85	0	0.0	
64 – 70	65	2	3.1	
>70	73	2	2.7	
Region lived in in the past year				0.137
East Asia	51	4	7.8	
Europe & US	11	0	0.0	
North Africa	62	0	0.0	
Other African Countries	41	1	2.4	
South Asia	91	4	4.4	
West Asia	48	0	0.0	
Level of education				0.614
No formal education	134	5	3.7	
Primary education	56	1	1.8	
Secondary education	63	1	1.6	
University-higher education	37	2	5.4	
Occupation				1.000
Health care worker	4	0	0.0	

Cont. **Table 13. Association between tuberculosis and demographic variables**

Variable	n	TB+ve	%	p
Miner	1	0	0.0	
Laboratory personnel	1	0	0.0	
None of the above	278	8	2.9	
Underlying health conditions				0.724
Yes	187	5	2.7	
No	101	4	4.0	
Chronic kidney disease				1.000
No	280	9	3.2	
Yes	8	0	0.0	
Chronic liver disease				1.000
No	283	9	3.2	
Yes	5	0	0.0	
Chronic lung disease				0.689
No	223	8	3.6	
Yes	65	1	1.5	
Cardiovascular disease				0.371
No	236	9	3.8	
Yes	52	0	0.0	
Hypertension				0.723
No	193	7	3.6	
Yes	95	2	2.1	
Cancer				1.000
No	287	9	3.1	
Yes	1	0	0.0	
Diabetes				0.451
No	219	6	2.7	
Yes	69	3	4.3	
Stroke				1.000
No	286	9	3.1	
Yes	2	0	0.0	

Cont. **Table 13. Association between tuberculosis and demographic variables**

Variable	n	TB+ve	%	p
Not Listed				1.000
No	269	9	3.3	
Yes	19	0	0.0	
Travel outside current country of residence in the past year				1.000
Yes	39	1	2.5	
No	251	8	3.1	
Hajj/Umrah (Past-year)				0.190
No	266	8	3.0	
Yes	21	0	0.0	
Don't recall	6	1	16.7	
Smoked				1.000
No	187	5	2.7	
Yes	93	3	3.2	
Any medication				0.745
No	171	6	3.5	
Yes	114	3	2.6	
Previous TB treatment				**0.015**
No	236	5	2.1	
Yes	12	2	16.7	
Don't know	24	2	8.3	
Cough in household				1.000
No	219	7	3.2	
Yes	33	1	3.0	
Don't know	4	0	0.0	
Close contacts TB patient				1.000
No	219	7	3.2	
Yes	5	0	0.0	
Don't know	33	1	3.0	
Cough up blood				0.562
No	224	7	3.1	
Yes	24	1	4.2	

Cont. **Table 13. Association between tuberculosis and demographic variables**

Variable	n	TB+ve	%	p
Cough length (Days)				0.461
<= 1 Week	164	4	2.4	
>1 to 2 Weeks	60	2	3.3	
>2 to 3 Weeks	14	1	7.1	
> 3 Weeks	25	1	4.0	
Admission ward				0.062
Other wards	13	0	0.0	
ER	89	2	2.2	
ICU	21	0	0.0	
General ward	79	0	0.0	
Isolation ward	83	6	7.2	
Surgical ward	10	1	10.0	

TB; tuberculosis, ICU; intensive care unit, ER; emergency room, US; United States of America

Table 14. Demographic variables and risk of tuberculosis

Variable	n	TB+ve	%	OR	95% CI		p
Gender							
Male	100	3	3.0	1			
Female	202	6	3.0	1.010	0.247	4.126	0.989
Age							
Mean (Range)							
<53	74	4	5.4	1			
53 – 63	85	0	0.0	-	-	-	0.997
64 – 70	65	2	3.1	.556	0.098	3.137	0.506
>70	73	2	2.7	.493	0.087	2.778	0.423
Region lived in in the past year							
Asia	190	8	4.2	1			
Europe & US	11	0	0	-	-	-	0.999
Africa	103	1	0.9	0.223	0.028	1.809	0.160

Cont…Table 14. Demographic variables and risk of tuberculosis

Variable	n	TB+ve	%	OR	95% CI		p
Level of education							
Some form of education	156	4	2.5	1			
No formal education	134	5	3.7	1.473	0.387	5.600	0.570
Underlying health conditions							
No	187	5	2.7	1			
Yes	101	4	4.0	0.666	0.175	2.538	0.552
Travel outside current country of residence in the past year							
No	251	8	3.1	1			
Yes	39	1	2.5	0.799	0.097	6.572	0.833
Hajj/Umrah (Past-year)							
No	266	8	3.0	1			
Yes	21	0	0.0	-	-	-	0.998
Don't recall	6	1	16.7	6.450	0.673	61.773	0.106
Smoked							
No	187	5	2.7	1			
Yes	93	3	3.2	1.213	0.284	5.191	0.794
Any medication							
No	171	6	3.5	1			
Yes	114	3	2.6	0.743	0.182	3.034	0.679
Previous TB treatment							
No	236	5	2.1	1			
Yes	12	2	16.7	9.240	1.593	53.588	**0.013**
Cough in household							
No	219	7	3.2	1			
Yes	33	1	3.0	.946	0.113	7.948	0.960

Cont... Table 14. Demographic variables and risk of tuberculosis

Variable	n	TB+ve	%	OR	95% CI		p
Close contacts TB patient							
No	219	7	3.2	1			
Yes	5	0	0.0	-	-	-	0.999
Don't know	33	1	3.0	0.946	0.113	7.948	0.960
Cough up blood							
No	224	7	3.1	1			
Yes	24	1	4.2	1.348	0.159	11.443	0.784
Cough length (Days)							
<= 1 Week	164	4	2.4	1			
>1 to 2 Weeks	60	2	3.3	1.379	0.246	7.732	0.715
>2 to 3 Weeks	14	1	7.1	3.077	0.320	29.576	0.330
> 3 Weeks	25	1	4.0	1.667	0.179	15.545	0.654
Admission ward							
Other wards*	212	3	1.4	1			
Isolation ward	83	6	7.2	5.429	1.325	22.242	**0.019**

*ER, ICU, General ward, Surgical ward, other

TB= tuberculosis, ICU= intensive care unit, ER=emergency room, US= United States of America, OR= odd ratio, CI= confidence interval

Table 15. Results of the multivariate analysis

Variable	aOR (95% CI)	p
Previous TB treatment		
No	1	
Yes	8.1 (1.351-48.464)	**0.022**
Admission ward		
Other wards*	1	
Isolation ward	3.0 (0.648-14.497)	0.158

aOR=adjusted odd ratio, CI=confidence interval, TB=tuberculosis

*ER, ICU, General ward, Surgical ward, other

2.6 Discussion

Since being declared a global emergency by the WHO in 1993, political and scientific advocacy as well as funder investments has resulted in a slow but steady progress in reducing the global TB case load and mortality rate (World Health Organization, 2018b, Zumla and Davies, 2016). Part of the reason for this slow progress is that a significant proportion of people who fall sick with TB are never diagnosed and treated. WHO estimates that 3-4 millionpeople who fall ill with TB each year are not diagnosed, not notified, or do not start treatment, leading to the persistence of infectious cases and disease transmission (World Health Organization, 2017b, 2018b). Many of those who do start treatment have a delayed start due to a range of challenges. These include HIV; having chronic cough and/or other lung diseases; negative sputum smear; *EPTB*; rural residence; low access (geographical or sociopsychological); initial visitation of a government low-level healthcare facility, private practitioner, or traditional healer; old age; poverty; female gender; alcoholism and substance abuse; history of immigration; low educational level; low awareness of TB; incomprehensive beliefs; self-treatment; and stigma (Storla et al., 2008). Delays in diagnosis and treatment of TB are also important factors in persistent transmission of the disease (Golub et al., 2006, Lin et al., 2008). Therefore, identification of individuals with TB and prompt initiation of effective treatment to rapidly render them non-infectious are crucial to stop transmission, prevent new infections and new TB cases, contributing to the global reduction in TB burden (Yuen et al., 2015).

Hajj represents many of the risk factors for transmission of respiratory infections including TB and reactivation of LTBI (Ahmed et al., 2006, Ai et al., 2016, Al-Orainey, 2013, Wilder-Smith et al., 2005). Little information is available on the prevalence of active TB among pilgrims during Hajj. Evidence of TB in pilgrims comes from clinical studies of causes of hospital admissions during Hajj which reported the isolation of *M. tuberculosis* from 5-28% of patients with pneumonia during the event (Alzeer et al., 1998, Madani et al., 2006, Mandourah et al., 2012). In any case, TB in seriously ill pilgrims is likely to be a great underestimation of the prevalence of TB in the general pilgrims' population, with many cases remaining undiagnosed even amongst hospitalised patients.

Many cases in which TB is co-morbid with non-communicable or other communicable diseases may be missed, and patients with undiagnosed active TB may not be investigated for TB because they are asymptomatic or do not meet the criteria for TB screening (Ayles et al., 2009, Bates et al., 2012, Onozaki et al., 2015).

2.6.1 Tuberculosis among non-hospitalised pilgrims

In Hajj, only one study conducted in 2015, reported undiagnosed active PTB among non-hospitalised pilgrims from high-burden TB countries (Yezli et al., 2017b). The study enrolled pilgrims from 5 countries: Afghanistan, Bangladesh, Pakistan, Nigeria and South Africa. While these countries have high-TB burden and many contribute large number of pilgrims to the Hajj, the study did not enroll other countries with significant pilgrim population and TB prevalence such as India and Indonesia. These 2 countries have a TB incidence of 204/100,000 and 319/100,000 (World Health Organization, 2018b), and a Hajj pilgrim population of around 150,000 and 170,000 respectively. In fact, Indonesia is the country with the largest Hajj pilgrim population accounting for around 13% of the Hajj international pilgrims. In addition, while the 2015 study did not report MDR-TB among the studied population (Yezli et al., 2017b), this population did not originate from countries with the highest MDR-TB rates in the world. The latter also send pilgrims to Hajj, comparatively in smaller numbers. Countries such as Tajikistan, Kazakhstan, and Kyrgyzstan collectively contribute around 8,000 pilgrims in Hajj and have a prevalence of MDR-TB among new cases of 20-26%. This prevalence is 5-14 times that of the countries included in the 2015 study.

We performed a large-scale screening for active PTB among non-hospitalised pilgrims with productive cough during the 2016 Hajj.The1,510 pilgrims screened originated from 16 countries in Africa, former Soviet countries and South Asia. The TB incidence rate for these countries ranges between 70-567/100,000 with a prevalence of MDR-TB among new cases of 1-26% (World Health Organization, 2018b). Seven of these countries (Bangladesh, India, Indonesia, Pakistan, Ethiopia, Nigeria and South Africa) are among the WHO’s top 30 high TB burden countries in the world (World Health Organization, 2017b, 2018b), hence representing the highest risk for TB transmission during Hajj. Combined, the 16 countries included in the study contribute around 820,000 pilgrims to Hajj each year (62% of the total international Hajj pilgrims).

Eight countries (Algeria, Bangladesh, India, Indonesia, Pakistan, Morocco, Nigeria and Sudan) are among the top 10 countries with the highest pilgrim population for Hajj. While other countries included in the study do not send large numbers of pilgrims to Hajj, they are important as far as TB epidemiology is concerned. For instance, South Africa only contribute around 2,400 pilgrims to Hajj but it has one of the highest TB incidence rates in the world at 567/100,000(World Health Organization, 2018b). Similarly, while countries like Tajikistan, Kazakhstan and Kyrgyzstan only contribute similar small number of pilgrims to Hajj, they have some of the highest MDR-TB prevalence rates in the world(World Health Organization, 2017b, 2018b).

The study found that 0.66% of pilgrims with productive cough from the enrolled countries had active PTB. This is lower than a2015 study which detected active PTB in 1.4% of the study population (Yezli et al., 2017b). If analysis of our results is restricted to pilgrims from only the 5 countries included in the 2015 study, the percentage of active PTB in that population would be 1%. The 0.66% rate found in the current study is within the lower end range of that found among migrants to low-incidence countries (0.1-10%) (Aldridge et al., 2014).Similarly, it is also within the higher end range of TB prevalence rates reported for national and large TB surveys among adult populations in High and medium burden TB countries in Africa and Asia (0.03-1.5%)(China Tuberculosis Control, 2004, Deribew et al., 2012, Hoa et al., 2010, Kapata et al., 2016, Kebede et al., 2014, Onozaki et al., 2015, Qadeer et al., 2016, Senkoro et al., 2016, Wang et al., 2014, Wei et al., 2014, Zaman et al., 2012, Zaman et al., 2006). Given the short time pilgrims spent in KSA at the time of enrolment in the study, it is likely that the identified active TB cases were imported or reactivation of LTBI. The 0.66% rate of active TB among pilgrims found in this study means that potentially 6 out of each 1,000 pilgrims from the countries enrolled symptomatic for cough could have active PTB during Hajj. This is concerning given that the estimated total number of pilgrims attending the Hajj from the 16 countries included in the study is around 820,000 pilgrims and the prevalence of cough among Hajj pilgrims was reported to be between 51 and 91% (Deris et al., 2010, Gautret et al., 2015, Gautret et al., 2009).

We detected active TB among pilgrims symptomatic for cough but not seriously ill to be hospitalised or require medical attention. This is in accordance with previous prevalence surveys conducted in endemic TB countries which have shown that an important proportion of infectious individuals with bacteriologically positive sputum do not experience symptoms of sufficient severity to prompt health-seeking behaviour (Ayles et al., 2009, Corbett et al., 2010, Hoa et al., 2010, Onozaki et al., 2015). For example, Ayles and colleagues reported that 2.8% (53/1,920) of people symptomatic for cough sampled from a province in Zambia, a country where TB and HIV are endemic, had *M. tuberculosis* in their sputum (Ayles et al., 2009).While the study reported that prolonged cough was associated with prevalent TB, out of these 53 TB cases, 17 had a cough of between one and 21 days. This suggests that screening only individuals who meet TB screening criteria of cough over two or three weeks may result in a sizable proportion of active TB cases to be missed (Ayles et al., 2009, Onozaki et al., 2015). Interestingly, eight out of the 79 (10%) TB-positive cases identified in the study denied having any symptoms at all and only 34 (43%) would have been classified as a TB suspect by current guidelines at the time of the study. Corbett et al.(Corbett et al., 2010) screened the sputum of 10,092 adult residents of suburbs of Harare, Zimbabwe, symptomatic for chronic cough (≥2 weeks). The prevalence of culture-positive TB was 0.65%, with only 3% of the participants reporting previous TB treatment. In general, TB prevalence surveys report undiagnosed TB in the community with 79-98% of the TB cases identified through these surveys not being on treatment at the time when the surveys were conducted (Hoa et al., 2010, Kapata et al., 2016, Kebede et al., 2014, Onozaki et al., 2015, Qadeer et al., 2016, Senkoro et al., 2016, Wood et al., 2007, Zaman et al., 2012). These TB prevalence surveys also found that 26-79% of the TB cases were asymptomatic or did not show symptom suggestive of TB such as chronic cough (Hoa et al., 2010, Kapata et al., 2016, Kebede et al., 2014, Onozaki et al., 2015, Qadeer et al., 2016, Senkoro et al., 2016, Wood et al., 2007, Zaman et al., 2012).

Most of the TB cases detected in the current study were in pilgrims from India (30%) and Afghanistan (20%). India has the second highest incidence of TB (319/100,000) (World Health Organization, 2018b) among the 16 countries included in the study and contributed the highest number of the enrolled pilgrims (15.24%).

Undiagnosed active PTB have been reported in the community in India. Rao et al.(Rao et al., 2012) conducted a community based cross-sectional TB survey that screened 95,071 individuals. Of these, sputum was collected from 7,533 individuals. The overall prevalence of bacteriologically positive PTB was 255.3/100,000 population (95% CI= 195.3–315.4). Of the total 221 bacteriologically positive PTB cases detected by the survey, only 73 (33.0%) were found to be on anti-TB treatment (Rao et al., 2012). While pilgrims from Afghanistan represented less than 6% of the study population, and the country has a TB incident rate lower than that of seven countries included in the study, it is highly represented among the active TB cases. A similar observation was reported in a previous study among non-hospitalised Hajj pilgrims, where 80% of undiagnosed active PTB cases were reported in pilgrims from Afghanistan (Yezli et al., 2017b). We hypothesize that political instability, conflicts and socioeconomic factors may be responsible for the results observed. Afghanistan is one of the poorest countries in the world with some of the lowest indicators of socioeconomic and human development indices ratings due to decades of conflict, political instability and lack of foreign investment. The WHO describes its health system as one of the worst in the world (World Health Organization, 2004). As a consequence, ,health services coverage and delivery, including TB services, may be limited resulting in TB cases being not diagnosed, notified or treated or in these processes being delayed which lead to persistent transmission (Golub et al., 2006, Lin et al., 2008, World Health Organization, 2017b, 2018b).

As per a previous report (Yezli et al., 2017b) undiagnosed active PTB was also identified in pilgrims from Bangladesh and Pakistan. In addition, cases were found among pilgrims from Indonesia, Somalia and South Africa. With the exception of Somalia, the above countries are among the WHO's top 30 high TB burden countries in the world. Interestingly, only one case of active PTB was found among pilgrims fromSouth Africa in the current study and none in a previous report (Yezli et al., 2017b). South Africa is among the top countries with the highest TB, MDR-TB and TB/HIV burdens in the world (World Health Organization, 2018b). The epidemiology of TB in the country is closely related to that of HIV and is regional and linked to socioeconomic, behavioural and demographic factors (Kenyon and Zondo, 2011, Nanoo et al., 2015, Shisana et al., 2014). Most of the Muslim population in South Africa are of Asian (mostly Indian) descent who represent around only 2.5% of the population.

The difference in the socioeconomic status, behavioural factors and lower prevalence of HIV among the different ethnic groups may explain the lower incidence of TB in the Muslim population compared to the overall population in South Africa and therefore the results observed in our study (Kenyon and Zondo, 2011, Muntingh, 2013, Shisana et al., 2014).

2.6.2 Tuberculosis among hospitalised pilgrims

This study performed the first screening for active PTB among hospitalised pilgrims with productive cough during the 2016 and 2017 Hajj seasons. The 347 inpatient pilgrims screened originated from 44 countries in Africa, Asia, Europe and the USA reflecting the diverse Hajj pilgrims population who come from up to 180 different countries (Yezli et al., 2017a). The 44 countries from which the study population originates from have a widely varied TB and MDR-TB incidence rates and include both low and high burden TB countries (World Health Organization, 2018b). Most countries represented among the study population were Indonesia, India, Bangladesh and Egypt. This is not surprising given that these countries are respectively ranked number 1, 3, 4 and 6 in the list of countries with the largest Hajj pilgrims' population. It is also worth noting that out of these 44 countries, 12 (27.2%) are among the WHO's top 30 high TB burden countries in the world (World Health Organization, 2018b).

The patients' population was also representative of the Hajj pilgrims' population in general, with over representation of older males with little or no formal education. Studies among non-hospitalised pilgrims reported similar observation. For example, in a screening of 1,1,64 Hajj pilgrims with productive cough, Yezli et al. (Yezli et al., 2017b) reported that that the mean age of the study population was 51.7 years with a male: female ratio of 2.6:1 Over half of the study population had no formal education. In another screening of 5,235 Hajj pilgrims from 22 countries, Memish et al. (Memish et al., 2014) reported the mean age of the study population to be 51.8 years and 54% were male. In general, elderly pilgrims represent a sizable proportion of the Hajj population (roughly 25% are at least 65 years old) (Ebrahim et al., 2009). Studies conducted among hospitalised Hajj pilgrims also report predominance of older males among inpatients with a mean age similar to that reported in the current study and slightly higher than reports from non-hospitalised pilgrims.

For example, a study among 266 inpatients with community-acquired pneumonia in Hajj 2016 reported the mean age of the study population to be 65.3 years and male: female ratio of 2:1 (AlBarrak et al., 2018). A similar study conducted in the 1994 Hajj among 64 patients, reported that 75% were men with a mean age of 63 years (Alzeer et al., 1998). In a study of all 808 admissions to hospitals at the Hajj holy sites during the Hajj dates of the year 2003, 62.5% were over 50 years old and 57.7% were males (Madani et al., 2006). In another report among 689 patients admitted to a hospital during the 2005 Hajj, the mean age was 62 years and the male: female ratio was 1.8:1(Khan et al., 2006).

Underlying health conditions were present among a sizable number of pilgrims with hypertension, diabetes and cardiovascular disease being among the most common conditions. This is in accordance with other surveys conducted among both hospitalised and non-hospitalised Hajj pilgrims (AlBarrak et al., 2018, Alzeer et al., 1998, Gautret et al., 2015, Khan et al., 2006, Madani et al., 2006, Mandourah et al., 2012, Memish et al., 2014, Shirah et al., 2017, Yezli et al., 2017b). However, the proportion of patients with underlying heath condition in the current study (65%) is higher than those reported previously. For instance, Yezli et al.(Yezli et al., 2017b) found that 27.7% of non-hospitalised pilgrims with cough had underlying health conditions, mainly hypertension, diabetes and cardiovascular disease. Only 4.4% of those with underlying health conditions suffered from chronic lung disease. This is in contrast with the current study where the proportion was 22.6%. However, this is not surprising given that the current study was focused on patients symptomatic for productive cough and most patients were admitted due to disease of the respiratory system. Gautret et al. (Gautret et al., 2015) reported that among 382 French pilgrims screened between 2012 and 2014, chronic disease was noted in 55.1%, including hypertension (30.2%), diabetes (27.5%), chronic cardiac disease (8.4%) and chronic respiratory disease (7.6%). Memish et al. (Memish et al., 2014) reported that hypertension and diabetes were found in respectively, 13.1% and 6.8% of the 5,235 Hajj pilgrims screened in 2013. In general, among hospitalised Hajj pilgrims higher proportions of patients with underlying health conditions were reported. For example, Madani and colleagues reported that among the 808 patients admitted to hospitals in the 2003 Hajj, 39.2% had co-morbid conditions (Madani et al., 2006). These were mainly diabetes (19.4%), hypertension (14.0%) and chronic obstructive pulmonary disease (COPD; 7.2%).

In another study conducted among 689 patients admitted to a tertiary care hospital during the 2005 Hajj, 31.9% had diabetes, 37.2% had hypertension, 31.8% had cardiac disease, and 14.9% had chronic lung disease (Khan et al., 2006). Among patients admitted for pneumonia, the reported prevalence of co-morbidities was over 40% (Mandourah et al., 2012). Among such patients the prevalence of diabetes, hypertension, COPD and cardiovascular disease were 34.1%, 32.5-36.4%, 7.17-35.9%, and 23.3% respectively (AlBarrak et al., 2018, Alzeer et al., 1998, Mandourah et al., 2012, Shirah et al., 2017).

Most (over 60%) of patients in the current study had an initial and/or final diagnosis of diseases of the respiratory system. This is not surprising given that the study targeted patients symptomatic for cough. Pneumonia was the most common admission/final diagnosis reported in over 40% of the patients. This is in accordance with many other studies that reported that pneumonia is a leading cause of hospital admission (accounting for 15–40% of hospital admissions) during the Hajj pilgrimage (Al-Ghamdi et al., 2003, Khan et al., 2006, Madani et al., 2006, Shirah et al., 2017). However, given that the current study enrolled patients with cough regardless of the admission diagnosis, other diagnosis were also recorded. Also, a significant proportion (28.1%) of patients were admitted to isolation wards. This follows the KSA MOH guidelines to prevent and control influenza and MERS. MERS causes acute respiratory distress syndrome and while its precise mode of transmission is still unclear, it does spreads through infected person's respiratory secretions such as through coughing and sneezing (Xiao et al., 2018). Thus, patients admitted to hospitals during Hajj symptomatic for cough and suspected of having MERS or influenza are isolated and investigated. In the current study, all patients admitted to isolation rooms were MERS or influenza H1N1 suspects. However, in the final diagnosis, none had MERS and 12% had H1N1. This is in accordance with previous reports showing lack of MERS-CoV carriage and infection among Hajj pilgrims but carriage and infection of some pilgrims with influenza H1N1 (Annan et al., 2015, Gautret et al., 2014, Hashem et al., 2019, Ma et al., 2017, Memish et al., 2014, Moattari et al., 2012, Ziyaeyan et al., 2012).

TB was suspected in 26 (9.4%) patients and was a final diagnosis in 5 (2.2%) cases. These observations are in accordance with other studies that have reported cases of TB among hospitalised pilgrims during Hajj, especially patients with pneumonia, the major cause of admission in the current study.

Alzeer et al. (Alzeer et al., 1998) reported that of 46 hospitalised patients with pneumonia during the 1994 Hajj, 13 (28%) had confirmed TB. Madani and colleagues Madani et al., 2006) performed a cross-sectional study of patients admitted to ICU in hospitals at Mina and Arafat during the 2003 Hajj. Sputum culture-confirmed TB was diagnosed in 5.9% of the 808 patients. Mandourah et al. (Mandourah et al., 2012) performed a prospective study of patients admitted to ICUs at 15 hospitals in Makkah and Madinah over two consecutive Hajj years, 2009 and 2010. Of the 452 patients studied, TB was diagnosed in 4.9%.

The results of the Xpert MTB/RIF assay showed that a number of TB cases were undiagnosed. Given the short time pilgrims spent in KSA at the time of enrolment in the study, it is likely that the identified active TB cases were imported or reactivation of LTBI. The results indicate that 2.9% of hospitalised Hajj pilgrims with productive cough had active PTB. These rates are higher than those reported for non-hospitalised pilgrims with productive cough from high-TB burden countries. In the latter population, active PTB was detected in 1.4% of the study population (Yezli et al., 2017b). The 2.9% rate found in the current study is within the range of that found among migrants to low-incidence countries (0.1-10%)(Aldridge et al., 2014), but higher than TB prevalence rates reported for national and large TB surveys among adult populations in high and medium burden TB countries in Africa and Asia (0.03-1.5%) (China Tuberculosis Control, 2004, Deribew et al., 2012, Hoa et al., 2010, Kapata et al., 2016, Kebede et al., 2014, Onozaki et al., 2015, Qadeer et al., 2016, Senkoro et al., 2016, Wang et al., 2014, Wei et al., 2014, Zaman et al., 2012, Zaman et al., 2006). Also, the current study found that the prevalence of undiagnosed or missed TB among the study population was 2.3%. This rate is close to that reported among patients with productive cough from a large referral hospital in a high TB and HIV burden country. In a hospital in Ethiopia, Assefa et al. (Assefa et al., 2019) screened 300 inpatients not diagnosed with TB for TB symptoms and tested their sputum for TB using smear microscopy and Xpert MTB/RIF assay. HIV status was documented for 198/300 (66%) of patients, 37 (18.7%) were found to be HIV positive. Using Xpert MTB/RIF assay, 10 (3.3%) of the sputum samples were positive for TB, with 4/10 also being smear positive. As with the current study, co-morbidity with diabetes was reported among the missed TB cases. However, while all TB positive cases found in the study by Assefa et al. (Assefa et al., 2019) had cough of over 2 weeks duration, in the current study, most cases (62.5%) had cough of less than 2 weeks duration.

This is in accordance with numerous reports indicating that an important proportion of individuals with active TB do not exhibit prolonged cough or other symptoms typical of TB. For example, community TB prevalence surveys from around the world report that 26-79% of TB cases identified were asymptomatic or did not show symptom suggestive of TB such as chronic cough (Hoa et al., 2010, Kapata et al., 2016, Kebede et al., 2014, Onozaki et al., 2015, Qadeer et al., 2016, Senkoro et al., 2016, Wood et al., 2007, Zaman et al., 2012).

In low-TB incidence countries such as Denmark and England, autopsy investigations reported the prevalence of undiagnosed TB among hospitalised patients to be from 0.1-3% (Juul, 1977, Roberts et al., 1971, Whittington, 1983). However, the prevalence is higher in low resources settings especially in high TB and HIV burden countries. For example, Kilale et al. (Kilale et al., 2013) reported that TB was detected in 33.8% of the 74 deceased individuals at a hospital in Tanzania. Bates et al. (Bates et al., 2012) reported that 13.4% of TB cases they identified among inpatients at a hospital in Zambia were unsuspected. In resource-limited settings of the Americas, south Asia and sub-Saharan Africa, post-mortem studies show that TB accounts for approximately 40% of HIV-related adult deaths and almost half of these TB cases are undiagnosed at the time of death (Cohen et al., 2010, Gupta et al., 2015, Wong et al., 2012). Screening of outpatients in South Africa with HIV infection for undiagnosed TB has shown rates of 12-20% (Bassett et al., 2010, Kufa et al., 2012, Lawn et al., 2011).

In the current study, most of the TB cases were in pilgrims from Indonesia (33.3%) and India (22.2%). Both these countries are high-TB burden countries with some of the largest pilgrims' populations (World Health Organization, 2018b). While these countries have ongoing NTPs, health services coverage and delivery, including TB services, may be suboptimal in certain areas. This results in TB cases being not diagnosed, notified or treated or in these processes being delayed which lead to persistent transmission (Golub et al., 2006, Lin et al., 2008, World Health Organization, 2017b, 2018b). Undiagnosed and delayed TB diagnosis have been reported from both India and Indonesia (Ahmad et al., 2011, Daulay et al., 2018, Rao et al., 2012).

In addition to Indian and Indonesia, TB cases were detected among patients originating from Nepal, Pakistan, Philippines and Sudan. Pakistan and the Philippines are also among the top 30 high TB burden countries according to the WHO, with the Philippines in particular having a high annual incidence rate for the disease. In 2017, the WHO estimated TB incidence rates in the Philippines and Pakistan were 554/100,000 and 267/100,000 respectively (World Health Organization, 2018b). Issues with TB diagnosis and management, including missed TB or delayed in diagnosis of the disease have been reported from Nepal, Pakistan, Philippines and Sudan (Dhungana et al., 2013, Elmadhoun et al., 2016, Laohasiriwong et al., 2016, Lopez et al., 2016, Mahato et al., 2015, Querri et al., 2017, Saqib et al., 2011, Saqib et al., 2018, Shuaib et al., 2018). Undiagnosed active TB among non-hospitalised Hajj pilgrims from Pakistan has also previously been reported (Yezli et al., 2017b).

2.6.3 Multi-drug resistant tuberculosis

MDR-TB considered as one of the greatest threats to TB control worldwide. Not only is the incidence of MDR-TB rising in many countries, each year the number of people developing active MDR-TB dramatically outpaces the number of people placed on MDR-TB treatment (Falzon et al., 2013). This expanding pool of individuals with untreated MDR-TB represents an important and underappreciated source of transmission especially in high-burden countries (Gumusboga et al., 2012, Moodley et al., 2011, Zhao et al., 2009).Transmission of MDR-TB is a serious concern as MDR-TB requires long (up to 2 years or longer), highly cost and extensive treatment with multiple, potentially toxic drugs and outcomes are poor (Orenstein et al., 2009). Among non-hospitalised pilgrims, no MDR-TB was identified, which is in accordance with a previous report mong the same population (Yezli et al., 2017b). While the study enrolled non-hospitalised pilgrims from countries with high prevalence of MDR-TB, the result should be interpreted in the context of the small number of TB cases detected.

Among hospitalised pilgrims, the study identified missed TB cases among hospitalised patients that were rifampicin-resistant and by proxy MDR-TB. Results showed that 0.65% of patients had rifampicin-resistant (potential MDR) TB. One case was missed completely, and another was diagnosed in the hospital as a TB case but not as an MDR-TB case.

This is a concern as the management of these cases as far as treatment and infection prevention and control (IPC) would not have been in accordance with MDR-TB management guidelines. While both cases were admitted to an isolation ward, and the case identified in the hospital as a TB case was referred to another hospital for further treatment at the end of the study period, the other undiagnosed MDR-TB was discharged. These cases could have been a source for both nosocomial and community transmission of MDR-TB. This is particularly relevant in the Hajj context where pilgrims from all over the world are in close contact for prolonged periods of time during the pilgrimage. Hence, as shown for other pathogens, this could lead to the globalization of MDR *M. tuberculosis* strains (Al-Tawfiq and Memish, 2015, Memish et al., 2015a).

While a previous study on undiagnosed TB among non-hospitalised Hajj pilgrims did not identify MDR-TB cases (Yezli et al., 2017b), there is evidence of MDR-TB during the mass gathering (Elhassan et al., 2017). Also, undiagnosed MDR-TB has been detected among hospitalised and non-hospitalised individuals in other communities. In a study from Zambia, 900 newly admitted adult patients able to produce sputum at a teaching hospital were screened for TB(Bates et al., 2012). Culture-confirmed TB was found in 22.4% of the inpatients, 13.4% of these (27/202) were non-TB suspects. Furthermore, there were 18 confirmed cases of MDR-TB in the study, five of which were unsuspected. Bates et al.(Bates et al., 2015) reported the results of whole-body autopsies conducted on inpatients who died in the adult inpatient wards at a hospital in Zambia. Among the 125 cases, 78 (62%) patients had TB, of whom 66 (85%) were infected with HIV. Among the 78 patients with TB, 20 (26%) were not diagnosed during their life and 13 (17%) had undiagnosed MDR-TB. Reports from Asia found that among TB cases detected in community TB prevalence surveys, up to 11% were MDR-TB (Onozaki et al., 2015).

2.6.4 Xpert MTB/RIF vs non-molecular techniques for diagnosing tuberculosis

Out of the 9 TB cases identified by Xpert MTB/RIF assay in the hospitalised pilgrims' cohort, 3 were also investigated by the hospitals using one or a combination of chest-X ray, sputum AFB and sputum culture, and 2 (66.6%) were diagnosed as TB cases. Also, among the 5 cases diagnosed as TB cases by the healthcare facilities, only 2 (40%) were positive using the Xpert MTB/RIF assay. Such observations have been reported from other studies.

Assefa et al. (Assefa et al., 2019) reported that among the 10 undiagnosed TB cases detected by Xpert MTB/RIF assay in their study, 40% were also smear positive. O'Grady et al. (O'Grady et al., 2012) reported that the Xpert MTB/RIF assay performs better than smear microscopy in an inpatient setting in a country where TB and HIV infection are highly endemic. Compared to the results of culture as the gold standard, the specificity of the Xpert MTB/RIF assay was 95.0% (95% CI= 92.4%–96.8%), and the sensitivity was 86.1% (95% CI= 80.3%–90.4%). In sputum smear–negative, culture-positive cases, the assay was 74.7% sensitive (95% CI= 64.6%–82.8%), identifying 71 additional TB cases that were not detected by smear microscopy. The sensitivity and specificity of the Xpert MTB/RIF assay for detecting culture-confirmed, RR-TB was 81.3% (95% CI= 53.7%–95.0%) and 97.5% (95% CI= 90.4%–99.6%), respectively. O'Grady et al. (O'Grady et al., 2012) and Mnyambwa et al. (Mnyambwa et al., 2017) however, found that despite the fact that the sensitivity of smear microscopy is inferior to both GeneXpert and mycobacterial culture, in their study, 64% of smear-positive sputa were negative in both GeneXpert and culture. In general, Xpert MTB/RIF assay has high sensitivity and specify. A meta-analysis of 16 studies gave a pooled sensitivity of 90% (95% CI= 89%–91%) and a pooled specificity of 98% (95% CI= 98%–99%) (Chang et al., 2012). Seven of these studies reported on the use of the Xpert MTB/RIF assay to detect rifampicin resistance. pooled sensitivity and specificity were 94% (95% CI= 92%–96%) and 97% (95% CI= 96%–98%), respectively (Chang et al., 2012). The assay is endorsed by the WHO (World Health Organization, 2010b) and has been successfully evaluated and used in a number of studies for identifying unsuspected TB among hospitalised and non-hospitalised patients (Bates et al., 2013, Bates et al., 2012, O'Grady et al., 2012, Yezli et al., 2017b).

2.6.5 Tuberculosis and gender

For non-hospitalised pilgrims, 60% of the TB cases identified were males, although there was no statistically significant difference in relation to gender and TB. However, the risk of TB was higher among females compared to males, although this was also not significant. Notwithstanding the small number of TB cases in our study, some studies reported similar results to ours (Araj et al., 2016, Codlin et al., 2011, Dogar et al., 2012). For example, TB screening in a rural Ethiopian community in 2009 found that among the undiagnosed PTB cases, there were more females than males (Deribew et al., 2012).

Similarly, reports from various areas of Pakistan indicate that the rates of notified TB cases are 20-30% higher in young females compared with males, and female rates remain high regardless of increasing age (Codlin et al., 2011, Dogar et al., 2012). On the other hand, for hospitalised patients, the prevalence of TB in the current study was similar among males and females (3%) and there was no significant increase in risk of TB among females compared to males. Bates et al. (Bates et al., 2012) also reported that the burden of unsuspected TB among patients in Zambia did not differ by gender. However, data on TB among patients detected during autopsy investigations suggest that the burden of undiagnosed TB is higher among males (Bates et al., 2015, Roberts et al., 1971, Whittington, 1983).

In general, worldwide, the male: female ratio of new TB cases is approximately 2:1. In 2017 the WHO reported that the global male: female ratio for notification was 1.7 (World Health Organization, 2018b). In contrast, the male to female ratio in 25 national TB disease prevalence surveys of adults in African and Asian countries implemented in 2007–2017 was about 2.5 overall, ranging from 1.2 (in Ethiopia) to 4.5 (in Vietnam) (Onozaki et al., 2015, World Health Organization, 2018b). Results from these surveys show higher burden of TB disease among men and also indicate that notification data understate the share of the TB burden accounted for by men in some countries. Also,men tend to have higher prevalence of undiagnosed TB than do woman (Ayles et al., 2009, Corbett et al., 2010).This gender disparity is even higher in TB prevalence surveys conducted worldwide (Borgdorff et al., 2000, Hoa et al., 2010, World Health Organization, 2018b) suggesting that the differences in notification rates may be largely due to epidemiological differences and not to differential access to health care (Borgdorff et al., 2000). This observation is supported by the results of reviews of qualitative evidence for gender-related differences in accessing TB services which reported that generally there were no gender-related differences in barriers and delays limiting access to TB services. When differences were identified, women experienced greater barriers and longer delays than men (Krishnan et al., 2014, Yang et al., 2014).

2.6.6 Tuberculosis and geographic area of residency and travel

For non-hospitalised pilgrims, there was no significant association between the geographic area of residence in the previous year (former Soviet countries, North Africa, Other African countries and South Asia) or travel outside the current country of residences in the previous year and TB. However, TB prevalence and risk of TB were higher among pilgrims from South Asia and those who travelled outside their country of residency in the previous year. The same observation was reported in a previous study among non-hospitalised Hajj pilgrims with cough (Yezli et al., 2017b). In the non-hospitalised pilgrims cohort, 66.7% of the countries in the "South Asia" category are among the top high-TB burden countries in the world compared to 60%, 0% and 0% for the "other African countries", "North Africa" and "former Soviet countries" categories respectively. In addition, over 48% of the non-hospitalised pilgrims enrolled in the study resided in South Asian countries. This may explain the higher TB prevalence among these pilgrims compared to other regions.

Similar observations were noted for hospitalised pilgrims. No significant association between the geographic region of residence in the previous year (Africa, Asia, Europe & US) or travel outside the current country of residences in the previous year and TB. However, TB prevalence and risk of TB were higher among hospitalised pilgrims from Asia, especially those from South and East Asia. In the hospitalised pilgrims' cohort, 62.5% of the patients originated from Asia. Also, among the 13 high TB burden countries represented among this cohort, 61.5% were Asian countries. This may explain the higher TB prevalence among patient from Asia compared to other regions.

In general it is known that travel to TB-endemic areas is a risk for TB (Bates et al., 2007). Yezli et al. (Yezli et al., 2017b) reported that Hajj pilgrims who travelled outside their country of residency were nearly twice as likely to have undiagnosed TB (OR= 1.90, 95% CI= 0.59, 6.04). While only 5.6% of non-hospitalised pilgrims reported travelling outside their countries in the previous year, over 28% of them travelled to India or Pakistan which are in the top 20 countries with the highest TB and MDR-TB burdens in the world (World Health Organization, 2018b). Among hospitalised pilgrims only 13.4% of patients travelled outside their country of residency in the previous year.

However, for both cohorts (hospitalised and non-hospitalised pilgrims) over 42% of those who travelled outside their country of residency in the previous year visited Saudi Arabia, specifically to perform Umrah and Hajj. The Umrah and Hajj mass gatherings have many similarities (Yezli et al., 2017a). While performing Umrah has not yet been linked to increase risk of TB infection, being involved in Hajj has (Wilder-Smith et al., 2005). Among non-hospitalised pilgrims, only one TB case reported traveling outside their country of residency in the previous year. This case travelled to Pakistan which is a high TB burden country (World Health Organization, 2018b). Similarly, for hospitalised pilgrims, one TB case reported traveling outside their country of residency in the previous year. However, this case travelled to Malaysia which is not a high TB burden country (World Health Organization, 2018b).

2.6.7 Tuberculosis and tobacco smoking

For non-hospitalised pilgrims, there was no significant association between tobacco smoking, whether active or in the past and TB. This is in accordance with a previous report from Hajj (Yezli et al., 2017b). For hospitalised pilgrims, while not statistically significant, there was an association between tobacco smoking and TB. Prevalence of TB was higher among smokers compared to those who never smoked (3.2% vs 2.7%) and smokers were 1.2 times more likely to have TB compared to non-smokers. This is in accordance with the strong evidence that smoking is significantly associated with TB. Smoking is associated with increased risks of TB infection and disease, TB mortality and recurrent TB (Bates et al., 2007, Khan et al., 2015, Lin et al., 2007). Also, TB patients who have smoked are more likely to transmit TB to their contacts (Godoy et al., 2013). In one study, smoking was associated with a 1.5 increased risk of LTBI among TB contacts and was estimated to be responsible for 12.8% of infections among this population (Godoy et al., 2013). In addition, exposure to environmental tobacco smoke and passive smoking increases the risks of TB infection and developing disease (du Preez et al., 2011, Lin et al., 2007, Sridhar et al., 2014). It is estimated that by 2050, smoking would lead to an excess of 18 million TB cases (Loddenkemper et al., 2016).

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 (Altet-Gomez et al., 2005, Leung et al., 2015, Masjedi et al., 2017). Smokers develop more extensive pulmonary disease, more lung capitation and cavitary lesions, more positive sputum smear and culture at the baseline and are more likely to require hospitalization (Altet-Gomez et al., 2005, Leung et al., 2015). For example, Leung et al. (Leung et al., 2015) assessed the impact of smoking on TB outcome among 16,345 consecutive patients undergoing chemotherapy for active TB in government chest clinics in Hong Kong from 2001 to 2003. These were followed up prospectively for 2 years for treatment outcome and subsequently tracked for relapse until the end of 2012. Smoking was associated with more extensive lung disease, lung cavitation and positive sputum smear and culture at the baseline. In both current smokers and ex-smokers, sputum smears and cultures were significantly more likely to remain positive after 2 months of treatment. Smokers (ex—or current) were significantly less likely to achieve cure or treatment completion within 2 years. Overall, 16.7% of unsuccessful treatment outcomes were attributable to smoking, with the key contributor being default in current smokers and death in ex-smokers. Among those who successfully completed treatment, there was a clear gradient (hazard ratios of 1.00, 1.33 and 1.63) of relapse risk from never-smokers to ex-smokers and current smokers, with an overall population attributable risk of 19.4% (current smokers: 12.2%; ex-smokers: 7.2%) (Leung et al., 2015).

2.6.8 Tuberculosis and underlying health conditions

At least 50% of the TB cases among non-hospitalised pilgrims had an underlying health condition, mainly hypertension (60%) and diabetes (40%). In a previous study, at least 33%of TB cases identified among non-hospitalised pilgrims had underlying health conditions (Yezli et al., 2017b). Among these, 40% had diabetes and 40% had hypertension. Similarly, at least 55.5% of TB cases among hospitalised pilgrims had an underlying health condition, mainly diabetes (60%) and hypertension (40%). A study of undiagnosed TB among 300 patients with productive cough in an Ethiopian hospital identified 10 missed TB cases, co-morbidity with diabetes was found in 10% of the TB cases(Assefa et al., 2019).

Among non-hospitalised pilgrims, TB was statistically significantly more prevalent among pilgrims with underlying health conditions and these were at a significantly higher risk of TB. Pilgrims with underlying health conditions were nearly 6 times more likely to have TB than those without an underlying health condition after adjusting for other variables. Yezli et al. (Yezli et al., 2017b) reported that TB was more prevalent among non-hospitalised Hajj pilgrims with underlying health condition and this population was an increased risk of TB. Although not statistically significant, pilgrims with underlying health conditions were over 2 times more likely to have TB. For hospitalised pilgrims, there was no association between co-morbidities and TB. However, underlying health conditions such as diabetes and chronic lung and kidney disease are known risk factors for TB (Marais et al., 2013), and there is a growing awareness of the influence of TB co-morbidity with these conditions as well as the burden of unsuspected TB (Bates et al., 2012, Young et al., 2009). For example, Bates and colleagues (Bates et al., 2012) reported the co-morbidity of diabetes, respiratory, renal and cardiovascular disorders with culture-positive TB in inpatients to be 21.1%, 15.5%, 10.5% and 3.2% respectively. The burden of TB was significantly greater in diabetes patients (OR= 6.6, p= 0.025).

The management of non-communicable disease is essential to reduce the burden of these diseases during Hajj as well as to reduce the burden of TB. For example, Pan et al. (Pan et al., 2015b) investigated the impact of diabetes prevention on TB morbidity and mortality in 13 high burden countries without a generalized HIV epidemic. The study found that stopping the rise in the prevalence of diabetes would prevent 6 million TB cases and 1.1 million TB deaths in the countries studied over 20 years. Aggressive interventions to reduce diabetes incidence would have an even larger impact on TB, avoiding 7.8 million cases and 1.5 million deaths. Given the above and the fact that around 15% of worldwide TB cases are attributed to diabetes, it was only right that the WHO has incorporated the management of diabetes into its strategy to decrease TB incidence by 90% by 2035 (The Lancet Diabetes, 2014).

2.6.9 Tuberculosis and age

Although not statistically significant, TB was more prevalent among non-hospitalised pilgrims in the older age groups and pilgrims in the youngest age group had the lowest risk of TB. After adjusting for other variables, non-hospitalised aged >55-64 were over 9 times more likely to have TB than those ≤45 years old (aOR= 9.5; 95% CI= 0.65-138.2), although this was not statistically significant. For hospitalised pilgrims however, there was no association between age and TB among inpatients, similar to what was reported by other(Bates et al., 2012). However, results of autopsy reports worldwide, suggest that undiagnosed TB among patients is more common among older individual (Juul, 1977, Katz et al., 1985, Roberts et al., 1971, Whittington, 1983). Observations from Hajj supports the notion that TB is more prevalent among older pilgrims and indicate that TB is commonly diagnosed among this population (Alzeer et al., 1998, Madani et al., 2006, Mandourah et al., 2012, Yezli et al., 2017b).For instance, Alzeer and colleagues (Alzeer et al., 1998) reported that the mean age of TB patients during the 1994 Hajj was 60 years. A study of undiagnosed TB among non-hospitalised Hajj pilgrims found that the prevalence of TB increased with age and that pilgrims aged over 64 years were 5.3 times more likely to be TB positive than those aged 47 years old or less (Yezli et al., 2017b).

Extremes of age are risk factors for TB(Marais et al., 2013), and the disease is generally more prevalent among older individuals as evidenced by the results of many TB surveys worldwide (Hoa et al., 2010, Onozaki et al., 2015, Qadeer et al., 2016). For instance, Hoa et al. (Hoa et al., 2010) reported that prevalence rate of smear-positive TB in Vietnam increased significantly with age, from 4.2/100,000 in the group aged 15-24 years to 429.3/100,000 in the group aged over 65. Similarly, studies from Tanzania, Bangladesh and Pakistan found that the highest TB prevalence was in the oldest age groups and increased with age(Qadeer et al., 2016, Senkoro et al., 2016, Zaman et al., 2012). A review of national TB prevalence surveys in Asia between 1990 and 2012 reported that age distribution pattern of TB cases was consistent with a progressive increase in rates of disease by age (Onozaki et al., 2015). In all countries investigated, the most recent surveys showed that TB prevalence rates peaked at the older age group of >65 years old. In Saudi Arabia, TB incidence also increase with age and are highest among the over 65 (Abouzeid et al., 2012, Al-Orainey et al., 2013).

The above findings are significant given that elderly pilgrims represent a sizable proportion of the Hajj population, with more than 50% aged over 50 years old and roughly 25% are at least 65 years old (Ebrahim et al., 2009).

2.6.10 Tuberculosis and level of education

Among non-hospitalised pilgrims, 80% of the TB cases identified had only primary or no formal education and TB prevalence in general was highest among this group, although the difference was not statistically significant. Similarly, for hospitalised pilgrims, 55.5% of the TB cases identified had no formal education and the latter population was at an increased risk of TB. Although not statistically significant, hospitalised patients with no formal education were 1.5 times more likely to have TB than those with some form of education. In a previous Hajj study, 86.6% of TB cases identified among non-hospitalised pilgrims had no formal education (Yezli et al., 2017b). Education was marginally significantly associated with the risk of TB after adjusting for other variables. Pilgrims with no formal education were nearly 4 times more likely to develop active TB than those with some form of education (aOR= 3.9; 95% CI= 0.98–16.0, P= 0.052)(Yezli et al., 2017b).

TB risk, prevalence and impact are 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 (Jurcev-Savicevic et al., 2013, Needham et al., 2001, Sanchez-Barriga, 2015). 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 (Sanchez-Barriga, 2015). In addition, low education is associated with poor knowledge of TB and attitude to the disease, which can facilitate transmissions and can lead to delaying health-seeking behaviour, lack of adherence to treatment regimes, treatment failure and disease complications and death (Gelaw, 2016).

2.6.11 Tuberculosis and previous tuberculosis treatment

Previous TB treatment was no commonly reported among the non-hospitalised pilgrims investigates with only 0.61% reporting previously being treated for TB. However, the treatment duration was less than 6 months in 25% of these pilgrims. Also, TB was much more prevalent among those who had been previously treated for TB (12.5% vs 0.6%, p= 0.054) and there was a significant increase in risk of TB in relation to previous TB treatment. Non-hospitalised pilgrims who reported having been treated for TB in the past were 30 times more likely to have TB compared to those who were not treated for TB (OR= 30.3; 95% CI= 4.19-219.0). Similar observations were found among hospitalised pilgrims, only 4.4% of whom reported previously being treated for TB. The treatment duration was less than 6 months in 41.6% of these pilgrims. In addition, among the 5 TB cases diagnosed by the healthcare facilities in this current study, 2 (40%) had previously been treated for TB. These 2 cases were also detected using the GeneXpert MTR/RIF assay. In a study from a hospital in Zambia, among the 27 unsuspected TB cases identified 5 (18.5%) had history of TB treatment(Bates et al., 2012). We report that TB was significantly more prevalent among hospitalised pilgrims who had been previously treated for TB and that the latter population was at a significant increase in risk of TB. Patients who reported having been treated for TB in the past were 8 times more likely to have TB compared to those who were not treated for TB after adjusting for other variables (aOR= 8.1; 95% CI= 1.35-48.4; p= 0.022).

Given the small number of TB cases identified in both hospitalised and non-hospitalised cohorts, it is difficult to draw conclusions from these results. However, it is well documented that inappropriate TB treatment is a serious concern and drives the occurrence of relapse and the emergence of drug-resistant TB (Fox et al., 1999, Hoffman et al., 2016, van der Werf et al., 2012, World Health Organization, 2014a). Treatment against TB may be inappropriate because: 1) the treatment duration is too short or the regimen contains too few drugs, has insufficient dose or drugs in a wrong combination; or 2) the duration of treatment is too long, with an excessive dose or number of drugs (Langendam et al., 2012). Inappropriate treatment of TB is common worldwide.

In a systematic review, Langendam et al. (Langendam et al., 2012) assessed the percentage of TB patients that received an inappropriate treatment regimen (type, dose, frequency of dosing and combination) from 37 studies from 22 countries, and one study was from multiple countries. Almost all continents were represented. Inappropriate treatment regimens were prescribed in 67% of the studies and the percentage of patients on inappropriate regimens varied between 0.4% and 100%. While the study did not investigate treatment duration, incomplete TB treatment is not uncommon. Although structural factors such as interruptions in drug supply play a role, patient default or drop-out from TB treatment is one of the most important reasons for not completing treatment (Borgdorff et al., 2002). One of the first reviews of adherence to TB therapy published in 1989 found non-adherence rates of 20–50%(Cuneo and Snider, 1989). More recent estimates of default rates in DOTS programs range from 6%to 30% (Balasubramanian et al., 2004, Jaiswal et al., 2003, Kaona et al., 2004, Zegeye et al., 2019).

2.6.12 Tuberculosis and contacts

Although not statistically significant, TB was more prevalent in non-hospitalised pilgrims who had close contacts diagnosed or treated for TB (4.2% vs 0.6%, p= 0.1599) and those who recently shared a household with an adult with cough (1.9% vs 0.7%, p= 0.1545). Having a close contact diagnosed or treated for TB significantly increased the risk of TB by 9 times (OR= 9.19; 95%CI= 1.49-56.4, p= 0.0166). In the multivariate analysis, those who recently shared a house with an adult with cough were 4.5 times more likely to have TB than those who didn't, after adjusting for other variables (aOR= 4.4; 95% CI= 1.01-19.5, p=0.047). Such associations were not observed among the hospitalised pilgrims. However, It is well documented that contacts of TB patients are a high-risk group for developing TB, particularly within the first year (Fox et al., 2013, Mendes et al., 2013, National Tuberculosis Controllers et al., 2005). Fox et al. (Fox et al., 2013) conducted a systematic review and meta-analysis of all studies reporting the prevalence of TB and LTBI, and the annual incidence of TB among contacts of patients with TB. In studies from low- and middle-income settings, the prevalence of active TB in all contacts was 3.1% (95% CI= 2.2–4.4%), microbiologically proven TB was 1.2% (95% CI= 0.9–1.8%), and LTBI was 51.5% (95% CI 47.1–55.8%).

The prevalence of TB among household contacts was 3.1% (95% CI= 2.1–4.5%) and higher among contacts of patients with MDR- or XDR-TB (3.4%; 95% CI= 0.8–12.6%). Incidence was greatest in the first year after exposure. In studies from high-income settings, the prevalence of TB among contacts was 1.4% (95% CI= 1.1–1.8%), and the prevalence of LTBI was 28.1% (95% CI= 24.2–32.4%).

Given the increased risk of TB among contacts, contact screening, as a strategy to identify recently infected individuals, is part of the TB elimination strategy (Mendes et al., 2013). It follows risk stratification concerning the infectiousness of the index patient, the duration and proximity of exposure, and the susceptibility of the contact (National Tuberculosis Controllers et al., 2005). In one study, older contact age (OR= 1.03, 95% CI= 1.02–1.05), cohabitation (OR= 4.26, 95% CI= 2.10–8.65), positive sputum analysis (smear or culture) (OR= 2.01, 95% CI= 1.06–3.82) and duration of the index patient symptoms (OR= 1.006, 95% CI= 1.001–1.011) were independent risk factors for positive screening (LTBI or TB) among contact. (Mendes et al., 2013). The study reported increased risk of *M. tuberculosis* transmission for households, which is already well documented (National Tuberculosis Controllers et al., 2005).

2.6.13 Tuberculosis and cough duration

Among the non-hospitalised pilgrims, there was a significant difference in TB prevalence in relation to cough duration (p= 0.0296), with pilgrims coughing between >1-3 weeks having the highest TB prevalence. Similarly, while not statistically significant, the risk of TB increased with increasing duration of cough. After adjusting for other variables, pilgrims who had symptoms >1-3 weeks were 1.8-3.8 times more likely to have TB than those who had cough for one week or less. Similar observations were found for the hospitalised pilgrims' cohort. In the latter, TB prevalence was higher among patients who had cough for over a week, with pilgrims with prolonged cough (>2 weeks) having the highest prevalence rates. Similarly, while not statistically significant, the risk of TB increased with increasing duration of cough. Compared to patients with a cough duration of less than a week, those coughing for >2-3 weeks had 3 times increase in the risk of TB.

Many studies have shown that an important proportion of infectious individuals with bacteriologically positive sputum do not experience symptoms suggestive of TB. In these studies from 40-79% of TB cases did not report TB symptoms that met screening criteria (generally cough of ≥2–3 weeks, and blood in the sputum) (Ayles et al., 2009, Hoa et al., 2010, Onozaki et al., 2015). However, cough is the most common symptom of PTB and is used as criteria for TB suspicion (World Health Organization, 2011a, 2013c). Lowering the cut-off duration for cough increases the sensitivity of cough-based symptomatic screening, but reduces the specificity of the screening method (Aleyamma et al., 2008, Santha et al., 2005). An Indian study showed a 23% rise in smear positive TB case detection using cough duration of ≥ 2 weeks for screening, in comparison with using cough duration of ≥ 3 weeks (Aleyamma et al., 2008).However, increased cough duration is correlated with TB. For example, Ayles and colleagues (Ayles et al., 2009), reported that prolonged cough was strongly associated with prevalent TB among individuals in Zambia. Having a cough of short duration (<21 days) was a risk factor culture-positive *M. tuberculosis* (aOR= 3.07, 95% CI= 1.62–5.81) but coughing for more than 3 weeks provided the strongest association with culture-positive *M. tuberculosis* (aOR= 12.72, 95% CI= 7.05–22.94).

2.6.14 Tuberculosis and admission ward for hospitalised pilgrims

In the bivariate analysis, patients admitted to an isolation ward were significantly more likely to have TB compared to those admitted to other wards (OR= 5.4; 95% CI= 1.32-22.2; p=0.019). After adjusting for other variables, patients admitted to an isolation ward were 3 times more likely to have TB compared to patients admitted to other wards, although this was not statistically significant. Given the inclusion criteria for the study and the context of the Hajj and the MERS prevention measures during this mass gathering, a large proportion of pilgrims were admitted to isolation rooms. Yet, a number of detected TB cases in the current study were admitted to other department such as ER and surgery ward. Undiagnosed TB cases were reported among patients not admitted to isolation wards including in general wards were IPC measures are less stringent, hence representing a higher risk for TB transmission. For example, in one study, among 300 patients not diagnosed with TB in a general medical ward in a large referral hospital in Ethiopia, 10 (3.3%) patients were found to have active PTB (Assefa et al., 2019). The above highlights the importance of strict adherence to IPC measures in healthcare facilities during Hajj, including in what is perceived as lower risk wards.

2.6.15 Results outcomes

The WHO and partners set out a post-2015 TB strategy with the goal of ending the global TB epidemic. The Sustainable Development Goals (SDGs) adopted by the UN in September 2015 covering the period 2016–2030 and the End TB Strategy endorsed by WHO's Member States at the 2014 World Health Assembly spanning a 20-year timeframe (2016–2035), aim to achieve this ambitious goal (World Health Organization, 2006a, 2015a). Targets set in the End TB Strategy are a 95% reduction in TB deaths and a 90% reduction in TB incidence by 2035 compared with 2015.The 2030 targets are a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate. The most immediate milestones, set for 2020, are a 35% reduction in TB deaths and a 20% reduction in the TB incidence rate, compared with levels in 2015 (World Health Organization, 2006a).TB prevention and control at Hajj is an important priority and will go a long way towards achieving the WHO post-2015 End TB Strategy goals (Zumla et al., 2016). This is because Hajj has been linked to the importation and globalization of respiratory pathogens as well as antimicrobial resistance determinants and the event is a risk for TB infection (Al-Tawfiq et al., 2016, Al-Tawfiq and Memish, 2015, Memish et al., 2015a, Wilder-Smith et al., 2005). Hence this mass gathering is likely to impact TB epidemiology in KSA and worldwide and TB during Hajj is a matter of global health security.

The results of the current study highlight the need for more attention toward TB and its burden during Hajj, including the issue of missed TB among hospitalised patients. This requires formulation and implementation of appropriate policies and interventions for early TB diagnosis, proper treatment and management as well as prevention of TB infection and transmission. In addition, training and education of HCWs to recognize symptoms of TB and implement appropriate screening strategies for early diagnosis of the disease are necessary. In the context of early diagnosis of TB among hospitalised patients, the introduction and use during Hajj of new and rapid point-of-care molecular diagnostic technologies such as the Xpert MTB/RIF assay and the now WHO endorsed next-generation Xpert Ultra (World Health Organization, 2017e) would be most beneficial. During Hajj, the healthcare system operates at near surge capacity with large volume of patients admitted to hospitals serving pilgrims.

Many of these pilgrims have respiratory symptoms, have co-morbidities and are keen to be discharged to continue their Hajj rituals. Short duration of hospitalization, and the masking of signs, symptoms and radiological findings by coexisting disease are documented contributing factors to failure to diagnose TB among patients (Roberts et al., 1971). The result of the study also highlight the importance of adherence to strict IPC measures in healthcare facilities during Hajj as nosocomial transmission of infection, including TB, during the mass gatherings may not only have implication on inpatients and HCWs but also on the larger pilgrims population, the local community and have global health security implications.

In addition, the results of the study suggest that 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 to rapidly render them non-infectious (Al-Orainey et al., 2013). Such TB screening programs are already in effect in a number of high-income, 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 towards arrivals from high TB-endemic countries (Aldridge et al., 2014). 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 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 countries most 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 are required. Nevertheless, the use of rapid point-of-care molecular diagnostic technologies such as the Xpert MTB/RIF and Xpert Ultra assays assay (World Health Organization, 2017e), would facilitate screening. While these diagnostic methods can be expensive, they may be subsidized in low-income countries to reduce the cost (World Health Organization, 2018b).

2.7 Study limitations

The current study has some limitations. In the non-hospitalised pilgrims' cohort we only screened 1,512 pilgrims from 16 countries which represent only a small proportion of the Hajj pilgrims' populations which exceeds 2 million and originates from over 180 different countries. The study detected a small number of TB cases among the population investigated. However, as many reports suggest that a sizable proportion of people with TB do not present with cough, the results may be an under estimation of the true prevalence of TB among non-hospitalised Hajj pilgrims. Future studies investigating a larger number of pilgrims from a greater number of countries with large pilgrims' populations and high TB and MDR-TB burdens such as Turkey, Egypt, China, Kenya, Myanmar, Russian Federation, Tanzania and Zambia, are warranted. Finally, while remote, we cannot eliminate the possibility that some of the non-hospitalised pilgrims investigated were already TB patients but chose not to disclose this information to the study investigators.

For the hospitalised pilgrims' cohort, the study only screened 304 inpatients symptomatic for cough. While the study systematically enrolled eligible patients, this number represents a small proportion of the total Hajj pilgrims admitted to healthcare facilities each year. Also, the study detected a small number of TB cases among the population investigated. Similar as above, numerous studies have reported TB cases among patients who were asymptomatic or did not have cough. Hence the reported prevalence of TB in the study may be an underestimation of the true prevalence of undiagnosed TB among hospitalised pilgrims in Hajj. On the other hand, the study population is not representative of the broader hospitals' population. Future studies investigating a larger number of patients may be warranted. Finally, for both cohorts, due to 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 (Marais et al., 2013).

2.8 Summary

In summary, the study conducted a large-scale screening for active PTB among non-hospitalised pilgrims attending Hajj. The study found that 0.66% of pilgrims with cough from high and medium TB burden countries (mostly from India and Afghanistan) had undiagnosed active PTB. Underlying health conditions and cough in the household were independent risk factors for TB after adjusting for other variables. The study also investigated for the first time the burden of undiagnosed active PTB among hospitalised pilgrims during the 2016 and 2017 Hajj seasons. It reports that among inpatients with cough admitted to hospitals serving Hajj pilgrims, 2.9% (mostly from Indonesia and India) had active PTB and most (77.7%) of these were missed by the hospitals including MDR-TB cases. Previous TB treatment was independent risk factor for TB after adjusting for other variables. 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 (Zumla et al., 2016). 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.

Chapter 3: Management of hospitalized pulmonary tuberculosis patients during the hajj Mass gathering

3.1 Executive summary

International travel, migration and movement of human populations facilitate the spread of Tuberculosis (TB). In this context, the Kingdom of Saudi Arabia (KSA) is particularly relevant because of its population dynamics and flow through the year as well as its hosting of mass gatherings such as the Hajj. The latter is an annual event in the Kingdom attended by over 2 million pilgrims from more than 180 different countries. As screening for TB is not a requirement for pilgrims before attending Hajj, potentially undiagnosed/untreated active TB brought to KSA during Hajj may have a major impact on the national and international epidemiology of TB. Hajj has been linked to increased risk of TB infection and both diagnosed and undiagnosed TB among pilgrims have been reported at the event. The TB management approaches during Hajj remained largely undocumented, and it is unknown whether these are consistent with the KSA and international TB management guidelines.

This study documents the management of TB patients during Hajj and explores the compliance of healthcare providers with the KSA TB management guidelines in the Ministry of Health (MOH) hospitals during the mass gathering. This to provide evidence base to optimize awareness, surveillance, screening, management and treatment, prevention, and control measures for TB during Hajj as well as other mass gatherings both within the Kingdom and worldwide.

The study used a cross sectional design to document the current TB management during the 2016 and 2017 Hajj seasons. The study was conducted over a one-month period (1-30thDulHija, Hajj lunar month) in hospitals in Makkah and holy sites including temporary hospitals operational only during Hajj days. Structured questionnaires were used to retrieve relevant indices on TB management from hospital records, healthcare providers and patients during the study period. The data was cleaned and analyzed in SPSS and results were presented as frequencies, percentages and means. A scoring system was developed to assess the compliance of health providers with key aspects of the KSA TB management guidelines.

There were 31 cases of drug-susceptible TB and 1 case of extensively drug-resistant TB (XDR-TB). Although the TB patients were nationals of 10 countries, 66.7% of them were KSA residents. Out of a maximum score of 10 for the selected TB management themes, the guideline compliance score was highest for infection prevention and control (IPC) and surveillance (9.6) and identifying TB suspects (7.2). The least scores were obtained for treating TB (5.0) and diagnosing TB (3.0). About half of the TB patients were separated from other patients at registration in the hospitals. The proportion of TB patients that were isolated in designated isolation rooms/wards rose from 77.4% pre-diagnosis to 96.7% on confirmation of TB diagnosis. All suspected TB patients were correctly screened using appropriate TB symptoms and chest X-ray was conducted for 67.7% of TB patients. Contrary to guideline recommendations, culture was the only diagnostic test applied in nearly 2/3rd of the TB patients. Smear microscopy was done sparingly, and no Xpert MTB/RIF assay was conducted for the TB patients. Additionally, only a fraction of TB patients were questioned about their Human Immunodeficiency Virus (HIV) status (20.7%) or tested for HIV (12.9%). Regarding treatment of drug-susceptible TB, only 37% of TB patients received four 1st-line anti-TB drugs, the majority received either three 1st-line anti-TB drugs (40.7%) or two 1st-line anti-TB drugs (11.1%). For TB notification, all confirmed TB cases with known notification status were reported to the KSA MOH, but the confirmed-TB status of two international pilgrims was not reported to their country health representatives/medical missions.

Based on observations from the current study a number of recommendations can be proposed. These are as follows:

- Develop and disseminate an international Hajj- and Umrah-specific TB control and management protocol to provide guidance on: TB surveillance, IPC, screening and diagnostic methods, choice of treatment and care models and patient transfer, including strategies for maintaining the continuum of care during and after the mass gatherings.
- Update the current KSA TB national guidelines to adopt new diagnostic recommendations and to highlight the treatment pathway for drug-resistant TB, in line with current global standards.

- Improve knowledge and practice of healthcare providers regarding TB management through the provision of training and periodic refresher courses as well as guidance materials.
- Monitor the TB management practices in MOH and non-MOH health facilities regularly to make recommendations for improvement.
- Provide the Xpert MTB/RIF Ultra assay testing capability at the point of care to facilitate same day TB diagnosis including MDR-TB.
- Raise awareness among healthcare providers about the need for mandatory screening and testing for HIV and other comorbidities in suspected TB patients.
- Consider conducting systematic/targeted TB screening for pilgrims arriving from within the Kingdom for the Hajj, based on a pre-established criteria.

3.2 Introduction and literature review

3.2.1 Introduction

Globally, there were an estimated 10.4 million new TB cases and 1.67 million deaths from tuberculosis (TB), in 2016 (World Health Organization, 2017b). Multidrug-resistant tuberculosis (MDR-TB) is defined as "the resistance of the TB bacteria to at least rifampicin (RIF) and isoniazid (INH)" (Falzon et al., 2011). In 2016, an estimated 490,000 new MDR-TB cases occurred globally(World Health Organization, 2017b). Despite past achievements in preventing TB morbidity and mortality, significant gaps in TB case detection and treatment success rates persist and undermine global TB control efforts. In 2016, the proportion of estimated new cases of drug-susceptible TB and MDR-TB that were detected were 61% and 22% respectively (World Health Organization, 2017b). The treatment success rate was 83% for drug-susceptible TB and 54% for MDR-TB (World Health Organization, 2017b). These figures show that a large proportion of TB infections remain undetected or untreated in the community and contribute to sustained community transmission of TB. The End-TB strategy aims to reduce the overall number of TB deaths by 95% and the TB incidence rate by 90% in 2035 compared with the 2015 baseline incidence and mortality figures (World Health Organization, 2015a).

One of the key pillars of the strategy is the integrated patient-centered care, which encompasses early diagnosis through systematic screening of high-risks groups and case-contacts, preventive treatment and vaccination, treatment for all people with TB and collaborative TB/HIV activities and management of comorbidities (World Health Organization, 2015a).

International travel, migration and movement of human populations facilitate the spread of TB. In this context, the Kingdom of Saudi Arabia (KSA) is particularly relevant because of its population dynamics and flow through the year as well as its hosting of mass gatherings such as the Hajj (Yezli and Memish, 2012). The latter is an annual event in the Kingdom attended by over 2 million pilgrims from more than 180 different countries(Yezli et al., 2017a). These pilgrims, mostly elderly, many from poor countries where TB is endemic, gather in close contact to perform physically challenging religious rites. Such conditions are ideal for transmission of respiratory infections including TB (Al-Orainey, 2013).

As screening for TB is not a requirement for pilgrims before attending Hajj, potentially undiagnosed/untreated active TB brought to KSA during Hajj (transmitted to other pilgrims, to local citizens and exported outside KSA) has potentially a major impact on the national and international epidemiology of TB. Hajj has been linked to increased risk of TB infection and both diagnosed and undiagnosed TB among pilgrims were reported (Al-Orainey, 2013, Alzeer et al., 1998, Alzeer, 2009, Wilder-Smith et al., 2005, Yezli et al., 2017b). Hospitals in Makkah serve both Hajj pilgrims as well as local residents and the Hajj workforce during the mass gathering free of charge. The additional stress on these health facilities during Hajj may compromise the services provided for all patients during the event, including those diagnosed with TB. No investigations were undertaken into whether the current KSA TB management guidelines during Hajj are followed in practice or if they are appropriate and effective for this unique event. This study documents the management of TB cases during the Hajj and explores the compliance of healthcare providers with the KSA TB management guidelines in the MOH hospitals during the mass gathering. This to provide evidence base to optimize awareness, surveillance, screening, management and treatment, prevention, and control measures for TB during Hajj as well as other mass gatherings both within the Kingdom and worldwide.

3.2.2 Literature Review

Chapter three is an overview of how TB patients admitted to the Makkah and holy sites hospitals were managed during the Hajj mass gathering and explore which guidelines the Saudi MoH followed to manage TB patients (pilgrims and non-pilgrims) during Hajj. Unfortunately, TB management approaches during this unique event remained largely undocumented, and it is unknown whether these are consistent with the KSA and international TB management guidelines. A search of electronic databases was conducted for relevant literature in English, without time restriction. Database searched included Pubmed, Scopus and Google Scholar. A combination of the MeSH terms and text words including: “Tuberculosis”, “TB”, “Pulmonary”, “Management”, “Treatment”, “Screening”, “Guideline”, “Patient”, “Pilgrim”, “Infection prevention and control” and “Diagnosis” were used. A manual search was also performed reviewing reference lists of identified literature to find additional papers. With few exceptions, only the most relevant and recent publications were used to develop the literature review. In addition, a review of both the World Health Organization (WHO) and KSA TB management guidelines was conducted to elucidate acceptable TB management approaches and to identify differences and similarities in national and global TB treatment strategies that may impact on TB management during Hajj and Umrah.

3.2.2.1 Early tuberculosis diagnosis through systematic screening of high-risks groups and case-contacts

Early detection through systematic screening of TB suspects is a major strategy for improving TB case detection. The WHO recommends that persons with signs and symptoms consistent with TB should be evaluated for TB to ensure prompt diagnosis and treatment (World Health Organization, 2011a, 2017a). Similarly, the Saudi TB guideline recommends that healthcare workers (HCWs) should be knowledgeable about TB symptoms to facilitate the efficient identification of TB suspects for diagnosis and treatment(Saudi Ministry of Health, 2014). In addition, both guidelines recommend that all close contacts of patients with pulmonary TB (PTB) should be screened for TB especially if they have signs and symptoms consistent with TB, are aged < 5years, have recognized or suspected immune compromising conditions or were in contact with patients with drug-resistant TB.

Systematic screening of people living with HIV and workers exposed to silica for active TB disease is mandatory, but priority should be given to other high-risk populations based on their contexts in terms of TB epidemiology, health system capacity, resource availability and the accessibility of the "at risk" populations. Some high risks groups for TB disease are enumerated in the KSA TB guidelines as: people with chronic diseases, such as diabetes mellitus and chronic renal failure; those with health conditions that require immunosuppressive or corticosteroid treatment; foreigners from countries with high TB disease burden; alcoholics and intravenous drug users; and people living in correctional facilities or prisons treatment (Saudi Ministry of Health, 2014). Several studies have shown that individuals with history of diabetes, tobacco-smoking related conditions, alcohol use, malignancies, silicosis and those on treatment with immunosuppressive medicines are at increased risks of TB disease (Cegielski and McMurray, 2004, Lönnroth et al., 2008, Rieder, 1999, Slama et al., 2007, Stevenson et al., 2007).

Cough is the most common symptom of PTB (World Health Organization, 2011a). Thus, a patient who presents to a health facility with history of cough of 2-3 weeks durations is expected to be screened for TB disease. Lowering the cut-off duration for cough increases the sensitivity of cough-based symptomatic screening, but reduces the specificity of the screening method (Aleyamma et al., 2008, Santha et al., 2005). An Indian study showed a 23% rise in smear positive TB case detection using cough duration of ≥ 2 weeks for screening, in comparison with using cough duration of ≥ 3 weeks (Aleyamma et al., 2008). Other symptoms that are useful for TB screening include hemoptysis, weight loss, fever and night sweats. As PTB screening tools, prolonged cough (lasting >2-3 weeks) has lower sensitivity (35%; CI: 24%-46%) and higher specificity (95%; CI: 93%-97%) than screening based on any cough duration (sensitivity: 57%; CI: 40%-74%, specificity: 80; CI: 69%-90%) and screening based on any TB symptom (sensitivity: 77%; CI: 68%-86%, specificity: 68; CI: 50%-85%), using culture-confirmed PTB as gold standard (Van't Hoog et al., 2013).

As another PTB screening tool, chest radiography has higher sensitivity, but less distinguishable specificity than symptom-based screening. The pooled sensitivity and specificity of chest radiography for PTB, using culture-confirmed PTB as gold standard is described as: for any chest radiography abnormality compatible with active or inactive TB (sensitivity: 98%; CI: 95%-100%, specificity: 75; CI: 72%-79%), chest radiograph abnormalities suggestive of active TB (sensitivity: 87%; CI: 79%-95%, specificity: 89; CI: 87%-92%) and chest radiography after positive screening for symptoms (sensitivity: 90%; CI: 81%-96%, specificity: 56; CI: 54%-58%) (Van't Hoog et al., 2013, World Health Organization, 2013c). Thus, the WHO recommends the use of chest radiography as a secondary screening test to enhance case detection, for all people with cough lasting more than 2 weeks, those who screened positive with TB symptoms and those with abnormal chest radiograph findings indicative of PTB (World Health Organization, 2013c, 2017a).

In the KSA TB guidelines, chest radiography is recommended as a non-diagnostic screening test for the following groups: people with positive tuberculosis skin test (TST) reaction (≥ 5mm induration), contacts with symptoms and signs of active TB, contacts with HIV infection, individuals with evidence of converting from negative to positive TST reaction within the past 2 years, those on treatment for latent TB infection (LTBI) who develop symptoms and signs of active TB, as well as children (under 5 years of age) who have a positive TST reaction(Saudi Ministry of Health, 2014).

3.2.2.2 Diagnosing active tuberculosis

The safe and efficient diagnosis of TB disease depend on the existence of an integrated network of multi-level laboratories with adequate biosafety standards, quality-assured capacity, mechanism for specimen referral and complimentary TB and HIV testing capability (World Health Organization, 2017a). In many settings with high TB burden, smear microscopy for acid fast bacilli (AFB), with 2 sputum samples is still the principal diagnostic testing method (World Health Organization, 2017a).

The standard application of 3 sputum samples for smear microscopy is not superior to 2-spot sputum sample collection technique, in terms of diagnostic sensitivity. Considering the clear advantage of a shorter diagnostic period, the 2-spot sputum collection method for smear microscopy is the current standard global practice (Mase et al., 2007, Rieder et al., 2005, World Health Organization, 2010a). Direct Ziehl-Neelsen stained sputum smear with conventional light microscopy is the most common and affordable method for PTB diagnosis, especially in low and middle income countries. Regular light microscopy has high specificity in areas with high TB burden but there is significant variability in its sensitivity (20-80%) for the detection of AFB in sputum samples. In comparison, conventional fluorescence microscopy is 10% (95% CI: 5–15%) more sensitive in detecting AFB in clinical specimens, has comparable specificity, and produces test results in significantly shorter time than light microscopy (Steingart et al., 2006, World Health Organization, 2015c). However, the widespread use of conventional fluorescence microscopy was hindered by the high cost of the required mercury vapour light sources and the additional requirement for regularly-maintained dark room (World Health Organization, 2011b).

As a result, the fluorescent light-emitting diode (LED) microscope was developed to increase the uptake of fluorescent microscopy, especially in resource limited settings. LED microscopy is relatively inexpensive, performs equally well in lighted rooms and is not associated with the emission of toxic mercury products if damaged (World Health Organization, 2011b, 2015c). In terms of diagnostic capacity, LED microscopy is 6% (95% CI, 0.1–13%) more sensitive than light microscopy and 5% (95% CI, 0–11%) more sensitive than conventional fluorescence microscopy in detecting AFB in clinical samples (World Health Organization, 2011b). Other comparative advantages of LED microscopy include reduced time to reading results, improved cost-effectiveness in resource limited settings and increased opportunity for integrated laboratory services based on its potential application for the diagnosis of other diseases, such as malaria and trypanosomiasis (World Health Organization, 2011b). Therefore, the WHO recommends the replacement of conventional fluorescence microscopy with LED microscopy in all settings where fluorescence microscopy is currently being applied for TB diagnosis (World Health Organization, 2011b).

The WHO also recommends a carefully phased implementation of LED microscopy as an alternative to regular light microscopy in all laboratories, using appropriate LED technology that meets approved specifications (World Health Organization, 2011b). Regardless, the general TB diagnostic applicability of sputum microcopy is limited by the need for quality assured laboratory processes, the inability to distinguish mycobacterium species and its relatively low sensitivity (World Health Organization, 2015c).

Generally, about eight organisms (*Mycobacterium tuberculosis, M.bovis, M.caprae, M. africanum, M. microti, M.pinnipedis, M. mungi, M. orgis and M. cannetti*) constitute the mycobacterium tuberculosis complex (MTB). These organisms are associated with variable spectrum of human and animal diseases, many of which are still poorly understood (Niemann et al., 2000).Thus, specie differentiation through solid or liquid culture is important for epidemiological considerations and for individualized patient management (e.g. *M. bovis* is generally resistant to PZA) (Kasper et al., 2015, World Health Organization, 2015c).Detection of mycobacterium species through culture provides a definitive diagnosis of TB. Compared to sputum microscopy, culture increases TB case detection by 30-50% (World Health Organization, 2015c). However, culture is not 100% sensitive for TB diagnosis because the decontamination procedures that limit the overgrowth of other microorganisms during sample processing for culture potentially have lethal effects on mycobacterium and hence compromise the yield of the bacteria during the procedure (World Health Organization, 2015c). Culture is also useful for monitoring response to MDR-TB chemotherapy and it is only recommended for high level and intermediate level facilities due to the additional skills and biosafety standards required for laboratory operations (World Health Organization, 2015c). In comparison with microscopy, culture is expensive, delicate and takes longer period to process samples and generate results. Liquid culture is less time-consuming and increases TB case detection by 10%, compared to solid culture (Organization and Organization, 2007).This advantage is however undermined by the relative high cost and additional biosafety measures required for liquid culture (Organization and Organization, 2007, World Health Organization, 2015c).

Both phenotypic and genotypic methods are available for the differentiations of cultured mycobacterium species (Niemann et al., 2000, Parsons et al., 2002).Strip tests for speciation (immunochromatographic assays) is the method of choice, since they can differentiate mycobacterium tuberculosis complex specie within 15 minutes (Organization., 2007).

The End-TB Strategy focuses on improving TB case detection rates, as one of the key strategies for TB control. Hence, molecular techniques are increasingly taking preeminence for TB diagnosis due to their rapid diagnostic speed and accuracy, as well as the reduced need for intensive biosafety measures. Xpert MTB/RIF is an automated real-time molecular diagnostic test that simultaneously detects drug-susceptible TB and RIF resistance (Nicol et al., 2013, World Health Organization, 2011c).The significantly reduced need for maintenance of extensive laboratory biosafety standards makes Xpert MTB/RIF a suitable diagnostic test for resource-limited TB endemic settings (World Health Organization, 2017a). In 2010, based on pooled evidence of Xpert MTB/RIF diagnostic accuracy, operational feasibility, cost-effectiveness and mean-time to TB detection, the WHO recommended the use of Xpert MTB/RIF, as initial TB diagnostic tests for people living with HIV and those suspected to have MDR-TB and for further testing of smear negative specimens (World Health Organization, 2011c).

With new evidence from Cochrane reviews, the 2010 recommendations was revised in 2013 to include conditional recommendations for the use of Xpert MTB/RIF, as initial TB diagnostic tests in all adults and children, rather than conventional microscopy and culture (World Health Organization, 2013a, 2014d). In the reviews, Xpert MTB/RIF had a pooled sensitivity of 88% (95% Credible Interval [CrI], 84-92%) and a pooled specificity of 99% (95% CrI, 98-99%), as an initial diagnostic test replacing sputum smear microscopy (Steingart et al., 2013, World Health Organization, 2013a). Additionally, Xpert MTB/RIF had a pooled sensitivity of 94% (95% CrI, 90-97%) and a pooled specificity of 98% (95% CrI, 97-99%) for the detection of RIF resistance (Steingart et al., 2013, World Health Organization, 2013a).

Xpert MTB/RIF was also proven useful for the diagnosis of other forms of TB. Compared to culture, the pooled sensitivities of Xpert MTB/RIF for various extra-pulmonary samples include: lymph node tissues/fluids (84.9%; 95% CrI, 72.1-92.4%), gastric fluid (83.8%; 95% CrI, 65.9-93.2%), cerebrospinal fluid (79.5%; 95% CrI, 62.0-90.2) and pleural fluid (43.7%; 95% CrI 24.8-64.7%) (World Health Organization, 2013a). The specificities of Xpert MTB/RIF for TB diagnosis using these extra-pulmonary samples range from 98.1%-99.9% (World Health Organization, 2013a). Nevertheless, most studies included in these reviews were conducted in highly controlled research laboratories. The evidence pooled from monitoring Xpert MTB/RIF performance in less-controlled settings is potentially a better indicator of the applicability and usefulness of Xpert MTB/RIF for TB diagnosis and the detection of RIF resistance.

To improve the sensitivity of molecular testing for the diagnosis of TB, especially in smear negative, culture positive TB cases and HIV positive TB cases, the Xpert MTB/RIF Ultra assay (Ultra) was developed by Cepheid Inc. Ultra was 5% (95% CI: +2.7, +7.8) more sensitive and 3.2% (95% CI: -2.1, -14.7) less specific than Xpert MTB/RIF, in a multi-center non-inferiority study (Bisallah et al., 2018). The difference in sensitivity was highest among smear-negative culture-positive patients (+17%, 95% CI: +10, +25) and among people living with HIV (+12%, 95% CI: +4.9, +21) (World Health Organization, 2017f). Based on the above evidence, the WHO now recommends Ultra, as the initial diagnostic test for all patients with signs and symptoms of PTB who are capable of producing sputum, as well as for the diagnosis of TB meningitis (World Health Organization, 2017a). Ultra is also recommended as the initial diagnostic test for detection of RIF resistance, and as an alternative for testing specific non-respiratory specimens from patients suspected of having extra-PTB (World Health Organization, 2017a).

Loop-mediated isothermal amplification for detecting TB is another molecular test, which is recommended by the WHO as an alternative test or a secondary test to smear microscopy for diagnosing PTB in adults with signs and symptoms of TB, in settings where conventional smear microscopy could be performed (World Health Organization, 2016b).

The lateral flow urine lipoarabinomannan assay is recommended to assist the diagnostic process for HIV positive patients with CD4 cell count <100 cells/µL, those with an unknown CD4 count and seriously ill HIV positive inpatients (World Health Organization, 2015e).

The growing burden of drug-resistant TB constitutes a significant challenge for TB control. Current control measures aim to rapidly detect drug-resistant TB cases and commence treatment to prevent TB complications and reduce further spread of drug-resistant TB in the community. To this end, the WHO recommended that drug-susceptibility testing (DST), using approved rapid tests should be performed for all new and retreatment TB patients, prior to commencing treatment (World Health Organization, 2017a). On detection of RIF resistance, the WHO recommends the use of rapid molecular tests to promptly detect the resistance to INH, fluoroquinolones and 2nd-line injectable agents to confirm diagnosis and inform treatment of MDR-TB and extensively drug-resistant TB (XDR-TB). The latter is defined as MDR-TB plus resistance to any fluoroquinolone and at least one of three injectable second-line drugs.2 Commercially available molecular line probe assays (LPAs) are preferred to phenotypic culture-based DST, as initial diagnostic tests to detect TB bacteria resistance to RIF and INH for persons with a sputum smear-positive specimen (direct testing) or a cultured MTB complex (indirect testing) (World Health Organization, 2016c, 2017a). In patients with confirmed RIF-resistant TB (RR-TB) or MDR-TB, molecular LPAs are preferred to phenotypic culture-based DST, as the initial test to detect resistance to fluoroquinolones and second-line injectable agents(World Health Organization, 2016d, 2017a).Culture-based phenotypic DST for selected anti-TB medicines should be performed for patients, who have initiated treatment for drug-resistant TB (World Health Organization, 2017a, 2018d).

3.2.2.3 Treating drug-susceptible tuberculosis

Starting TB treatment early and ensuring people with TB stay on treatment for the entire duration of treatment is a global TB control strategy. Drug-susceptible TB is curable, but inappropriate regimen prescription and non-adherence to recommended dosages contribute to poor treatment outcomes.

The WHO recommends the administration of standardized first-line anti-TB treatment regimen, consisting of an initial 2 months of treatment with INH, RIF, PZA and EMB and subsequently treatment with INH-RIF for the next 4 months. The 6 months TB treatment regimen is recommended for TB patients with drug-susceptible TB, those without prior history of starting treatment with anti-TB agents and those without recognized risk factors for drug resistance, while awaiting DST results (World Health Organization, 2017a, 2017c).Global TB control target is to reduce the duration of TB treatment to promote anti-TB drug compliance and reduce the exposure of patients to drug adverse events. As a result, the efficacy of a shorter (4 months) fluoroquinolone-containing anti-TB regimen was explored in various studies (Gillespie et al., 2014, Jindani et al., 2014, Merle et al., 2014). Higher relapse rates of the shorter fluoroquinolone-based regimen at 18 months follow-up, compared with the standard 6-months anti-TB regimen hindered its subsequent endorsement by the WHO (World Health Organization, 2017c).

Latest evidence suggest that fixed-dose combination (FDC) therapy for TB is as effective as single-drug formulations in terms of treatment outcomes (Gallardo et al., 2012). Considering some potential benefits of FDC-based TB regimen, which includes improved supply management, simplified prescription plan and increased patient satisfaction with reduced pill burden, the WHO recommends the administration of FDC formulations in the treatment of drug-susceptible TB (World Health Organization, 2017c).

The reduced pill burden of FDC regimen may be particularly useful for children who have difficulty ingesting multiple drugs and TB patients who are on other medications, such as HIV patients. In some settings, intermittent dosing gained popularity as a strategy for improving treatment adherence and reducing the impact of daily, directly observed treatment (DOT) on the health system (World Health Organization, 2017c). Indeed, intermittent (thrice weekly) dosing was recommended in 2010 by the WHO, as alternative choice wherever optimal daily dosing was unfeasible (Menzies D. et al., 2009, Mwandumba and Squire, 2001, World Health Organization, 2010d). However, concerns about higher risks of treatment failures, relapse and acquired drug-resistance led to the suspension of intermittent dosing as an alternative choice to optimal daily dosing, in 2017 (World Health Organization, 2017c).

Hence, the current recommendation specifies the use of the optimal daily dosing strategy in the treatment of all TB patients with drug-susceptible TB (World Health Organization, 2017c).

The KSA TB guideline is largely comparable to the aforementioned 2010 WHO guidelines for the treatment of drug-susceptible TB. The KSA guideline stipulates optimal daily dosing and the conventional 6 months treatment duration for drug-susceptible TB (Saudi Ministry of Health, 2014). It also makes provision for thrice weekly dosing in the continuation phase or throughout the entire duration of treatment, when daily dosing is not feasible (Saudi Ministry of Health, 2014). Like previous WHO guidelines, the 2014 KSA TB management guideline also recommended that the 8-months retreatment (CAT II) regimen, which included daily streptomycin (STM) injections in the intensive phase (2 INH-RIF-PZA-EMB-STM/ 1 INH-RIF-PZA-EMB) and 5 months exclusively-oral anti-TB agent in the continuation phase (5 INH-RIF-EMB) should be administered to relapsed and defaulted TB patients, while awaiting DST result (Saudi Ministry of Health, 2014). However, empirical treatment of such cases with CAT II regimen rather than performing DST to inform treatment choice leads to delays in commencing standard treatment for drug-resistant TB and unduly exposes TB patients to the toxic effects of STM (Gegia et al., 2017, Menzies Dick et al., 2009, World Health Organization, 2017c). Besides, the addition of STM to a previously failed TB regimen, which defines the CAT II regimen potentially propagates the development of resistance and culminates in the loss of STM as a 2nd line anti-TB drug (World Health Organization, 2017c). Thus, the WHO currently prohibits the prescription of CAT II regimen for TB retreatment and stipulated that DST should be performed to guide the choice of an appropriate TB treatment regimen in patients who require retreatment for TB (World Health Organization, 2017c). The use of adjuvant corticosteroid is indicated for the treatment of extrapulmonary TB (Saudi Ministry of Health, 2014, World Health Organization, 2017c). In TB meningitis, anti-TB therapy with adjuvant steroids are associated with reduced risks of disability, severe adverse events, relapse and mortality (Prasad et al., 2016, Thwaites et al., 2004, World Health Organization, 2017c). Similarly, adjuvant steroid administered with anti-TB treatment for the management of TB pericarditis improves treatment adherence and reduces the risk of death and complications, such as constrictive pericarditis (Wiysonge et al., 2017, World Health Organization, 2017c).

In TB patients living with HIV, early commencement of antiretroviral treatment (ART) improves wellbeing and reduces mortality. Various studies showed a link between “early” ART (initiated before 8 weeks of commencing anti-TB treatment) and the reduction in overall mortality, regardless of CD4 cell count (Blanc et al., 2011, Mfinanga et al., 2014, Yan et al., 2015). In addition to reduced mortality, “earlier” ART (commenced within 2 weeks of commencing anti-TB treatment) is associated with reduced risks of Acquired Immunodeficiency Syndrome (AIDS)-defining illnesses (Havlir et al., 2011). Nonetheless, both “early and earlier” ART, as opposed to delayed ART (commenced after 8 weeks of onset of anti-TB treatment), are associated with a higher risk of immune reconstitution inflammatory syndrome (IRIS) (Naidoo et al., 2012). Since potential benefits outweigh risks, the WHO recommends that TB patients living with HIV should receive appropriate anti-TB treatment initially and then ART should be commenced within the first 8 weeks of TB treatment (World Health Organization, 2016a). For patients with CD4 cell counts <50 cells/mm3, ART should be commenced within the first 2 weeks of commencing anti-TB treatment (World Health Organization, 2016a).

3.2.2.4 Treating drug-resistant tuberculosis

The transmission of drug-resistant TB, in various TB endemic settings, presents additional challenges for global TB control. Compared with drug-susceptible TB, the treatment of drug-resistant TB often involves prolonged treatment courses, use of potentially toxic drugs and poor treatment outcomes. The common forms of drug-resistant TB include INH-resistant TB, RR-TB, MDR-TB and XDR-TB. RIF-susceptible, INH-resistant TB is an emerging threat, which accounts for about 8% of TB cases worldwide (World Health Organization, 2017b, 2018e). Previous recommendations for INH-resistant TB treatment were based on expert opinion due to lack of evidence base (Jaramillo, 2008, World Health Organization, 2006b). In 2017, based on a systematic analysis of individual patient’s data, the WHO recommended that patients with confirmed RIF-susceptible, INH-resistant TB should receive RIF-PZA-EMB and levofloxacin for a duration of 6 months (World Health Organization, 2018e).

The conventional treatment choice for RR-TB and MDR-TB are the same and involves the use of 2nd-line anti-TB drugs in appropriate regimen (World Health Organization, 2016e). The Saudi guideline for the treatment of drug-resistant TB is limited to a general provision that recommends commencing empirical MDR-TB regimen upon the detection of RIF resistance and subsequent regimen adjustment in accordance with DST result. The provision makes no reference to the type and dosage of anti-TB drugs that should be considered in the composition of the MDR-TB regimen (Saudi Ministry of Health, 2014). In contrast, the WHO's 2011 guidelines for the programmatic management of drug-resistant TB specified the inclusion of at least four 2nd-line anti-TB drugs in a regimen consisting of PZA, one fluoroquinolone, one injectable agent, EMB (or prothionamide) and cycloserine (or para aminosalicylic acid) in the treatment regimen for MDR-TB (Falzon et al., 2011).

The 2011 guidelines also indicated that new MDR-TB cases should receive the appropriate regimen for 20 months, including an intensive phase of 8 months. Overall, none of the cohorts included in the meta-analysis used for development of the 2011 guidelines stemmed from randomized control trials. Secondly, substantial risk of bias was attributed to under-representation of some geographical areas in the included studies and the tendency for certain drugs to be reserved for the treatment of patients who have severe clinical disease (Akçakir, 2009, Johnston et al., 2009, Orenstein et al., 2009). Ever since, the effectiveness of a shorter MDR-TB treatment regimen which potentially offers superior cost-effectiveness and less exposure to the toxic side effects of chemotherapy has been explored in various studies (Kuaban et al., 2015, Nunn et al., 2014, Piubello et al., 2014, Van Deun et al., 2010). Pooled data analysis from these studies showed that patients who received the shorter MDR-TB regimen have higher likelihood of treatment success than those who received longer regimens (90% versus 78%) (Falzon et al., 2017). For patients receiving the shorter MDR-TB regimens, who have additional resistance to PZA and/or fluoroquinolones, the observed proportion of treatment success was lower but exceeded (without statistical significance) those on longer MDR-TB regimen.

Accordingly, the WHO updated the guidelines for the programmatic management of drug-resistant TB in 2016. The update includes the approval of a shorter MDR-TB regimen of 9–12 months, as potential replacement for the longer regimens in the treatment of RR-TB or MDR-TB, for patients having no prior treatment exposure to 2nd-line anti-TB drugs and those with excluded or highly unlikely risk of resistance to fluoroquinolones and 2nd-line injectable drugs (Falzon et al., 2017). This recommendation is applicable to adults and children with RR-TB and MDR-TB, regardless of their HIV status. However, the use of a shorter MDR-TB regimen is contraindicated in pregnancy and for the treatment of extra PTB (Falzon et al., 2017).

In cases where the shorter MDR-TB regimen is not applicable, an individualized regimen comprising of at least five effective anti-TB drugs in the intensive phase and four drugs in the continuation phase should be administered for 20 months or more (Falzon et al., 2017). The five drugs in the intensive phase should comprise of PZA, one drug each selected from group A and B and at least two drugs selected from group C (Table 16). The use of D2 and D3 drugs may be considered, if the regimen cannot be constituted as described above (Falzon et al., 2017). Bedaquiline and delamanid may improve treatment outcome in longer regimens, but usage beyond 24 months is not recommended due to uncertainties about their safety and efficacy beyond this period (Gler et al., 2012, Pontali et al., 2016, World Health Organization, 2017a).

Partial resection surgery is a recommended adjunct to standard MDR-TB regimen, since it is associated with improved treatment success for MDR-TB (Falzon et al., 2017, Harris Rebecca C et al., 2016). However, careful assessment of the individual patient's fitness for surgery, the state of surgical facilities and the availability of highly skilled surgeon should be considered before decisions are made to perform partial resection surgery (Falzon et al., 2017).

Table 16. Classification of 2nd-line anti-tuberculosis drugs

Group	Composition
Group A. Fluoroquinolones	Levofloxacin,
	Moxifloxacin,
	Gatifloxacin
Group B. Second- line Injectable agents	Amikacin,
	Capreomycin,
	Kanamycin,
	(STM)
Group C. Other core second-line agents	Ethionamide (or Prothionamide),
	Cycloserine (or Terizidone),
	Linezolid,
	Clofazimine
Group D. Add on agents	
D1	PZA
	EMB
	High-dose INH
D2	Bedaquiline,
	Delamanid
D3	Aminosalicylic acid,
	Imipenem–Cilastatin,
	Meropenem,
	Amoxicillin clavulanate
	(Thioacetazone)

INH= isoniazid, EMB= ethambutol, PZA= pyrazinamide, STM= streptomycin

3.2.2.5 Monitoring tuberculosis treatment and enhancing surveillance

Both the WHO and KSA TB guidelines recommend that all patients with PTB being treated with the 1st-line regimen should have their sputum samples tested by the end of the 2nd, 5th and 6th month of treatment (Saudi Ministry of Health, 2014, World Health Organization, 2010d). The WHO guideline also recommends that DST should be performed to detect resistance to at least RIF, if sputum samples remained smear positive or culture positive at the end of the 2nd month of treatment(World Health Organization, 2010d).

The KSA guideline differs slightly; it stipulates that a repeat sample should be collected and tested at the end of the 3rd month, if the initial sample collected at the end of the 2nd month of treatment remained smear positive (Saudi Ministry of Health, 2014). Culture and DST are indicated to detect resistance, if repeat samples collected at the end of the 3rd month remained smear positive (Saudi Ministry of Health, 2014).

Treatment monitoring standards for MDR-TB are well-highlighted in the WHO guidelines but there are no apparent provisions in the Saudi guidelines regarding treatment monitoring for MDR-TB (Falzon et al., 2017, Saudi Ministry of Health, 2014). In patients with MDR-TB, smear microscopy and culture are recommended by WHO, rather than smear microscopy alone, for treatment monitoring (Falzon et al., 2011, World Health Organization, 2014a). Generally, monthly smear-microscopy and sputum culture throughout treatment are the preferred monitoring choice (World Health Organization, 2014a). However, resource constrained settings could perform monthly smear microscopy and sputum culture until culture conversion, and subsequently reduce the frequency of performing culture to every alternate month (World Health Organization, 2014a). Daily assessment by clinicians is recommended in the first week for hospitalized MDR-TB patients on treatment and weekly for outpatients, until the treatment is well-tolerated. Afterwards, clinical assessment should be performed monthly or twice monthly.

In the continuation phase, except otherwise indicated by medical reasons, the DOT supporter should visit the patient daily to monitor adherence and tolerance and discuss any concerns with the physician/clinician (World Health Organization, 2014a). Weight monitoring (baseline, twice weekly for 3 months, then monthly throughout treatment) and height measurement (at the start of treatment) is required for BMI calculation. In children, monthly height measurement is indicated for monitoring growth (World Health Organization, 2014a). Chest X-ray should be performed at baseline and 6 monthly afterwards (World Health Organization, 2014a). For 1st-line and 2nd-line anti-TB drugs, DST should be performed at baseline and repeated for MDR-TB patients who remain culture positive or revert after the 4th month of commencing treatment (World Health Organization, 2014a).

Global TB policy mandates all providers to report both new and retreatment TB cases, including treatment outcomes, to their national public health authorities (World Health Organization, 2013b). In Saudi Arabia, TB is a notifiable disease for immediate reporting once the decision to commence treatment is taken. The legal framework authorizes the regular enforcement and evaluation of mandatory and timely reporting by providers, laboratories and hospitals (Saudi Ministry of Health, 2014). Electronic case-based reporting has replaced paper-based notification system in many settings. Electronic reporting promotes timeliness, ensures improved data access and reduces errors, such as duplication of data (World Health Organization, 2012). The most common variables used for TB reporting includes demographic data, prior TB treatment history and the current TB treatment information (World Health Organization, 2012).

3.2.2.6 Supportive approaches for tuberculosis management

Effective triage management that involves prompt detection of persons with TB symptoms and separation of TB suspected patients from others in a well-ventilated area is standard global practice (World Health Organization, 2009b). Patients who are immunosuppressed, such as HIV patients should be separated from those with suspected or confirmed infectious TB. Furthermore, patients with suspected or confirmed drug resistant TB should be separated from other TB patients, especially on the basis of their drug resistance profile (World Health Organization, 2009b). Upon separation, TB suspects should be educated about good cough etiquette and respiratory hygiene and be given priority considerations for prompt TB testing. Use of physical barriers, such as handkerchiefs, piece of tissue and surgical masks are preferred methods for promoting good cough and sneezing etiquette, if these materials are properly disposed of use. In the absence of physical barriers, the bend of the elbow and hand may be used to cover the mouth and nose when sneezing or coughing, but ensuring immediate cleaning afterwards is paramount (World Health Organization, 2009b).

Similarly, the Saudi national guideline for TB recommended the implementation of a symptom-based screening protocol for patients presenting with cough and respiratory symptoms in healthcare settings (Saudi Ministry of Health, 2014). Suspicious cases so identified are required to wear a surgical facemask and be immediately separated from others in a private examination room (Saudi Ministry of Health, 2014). Staff accessing such waiting areas and those in contact with infectious TB cases are advised to wear a National Institute for Occupational Safety and Health (NIOSH)-approved and fit-tested N95 respirator (Saudi Ministry of Health, 2014). It is unclear to what extent the use of surgical facemasks contributes to reducing nosocomial transmission of TB, but there are strong hypothetical considerations justifying the use of surgical mask, especially when infectious patients come in contact with vulnerable individuals (World Health Organization, 2009b). The WHO also recommends the use of particulate respirators by staff and visitors in enclosed space with infectious TB patients, health workers caring for suspected or confirmed MDR-TB and XDR-TB patients, as well as those engaged in aerosol-generating procedures associated with increased risk of TB transmission, such as intubation and bronchoscopy. Particulate respirators are not recommended for use by TB patients (World Health Organization, 2009b).

Adequate natural ventilation enhanced by using large-sized windows that are located on opposite walls is an important IPC measure in healthcare facilities. In areas with insufficient natural ventilation, mixed-mode ventilation using appropriate fans may be useful for maintaining adequate air dilution. Mechanical ventilation may be considered in settings with insufficient natural and mixed-mode ventilation systems, but systems that maintain adequate air changes per hour should be prioritized. In areas where climatic factors (e.g. cold, hot), infrastructural designs and high TB transmission associated morbidity and mortality risks (e.g. MDR-TB wards) exist and prevent the maintenance of adequate ventilation, complementary use of upper room or shielded ultraviolet germicidal irradiation devices are recommended (World Health Organization, 2009b).

Both the KSA and WHO TB guidelines consider the pursuit of a patient-centered approach to TB treatment, a necessary strategy for promoting treatment adherence, improving the quality of life of TB patients and alleviating suffering (Saudi Ministry of Health, 2014, World Health Organization, 2017a). Before initiating treatment, a rapid needs assessment is required to inform interventions (including combinations of psychological and material support, patient and staff education, tracer and use of medication support) that ensure treatment adherence and hence impact positively on outcomes (World Health Organization, 2009b, 2017a). Considering the cost effectiveness of community-based approaches and the reduced risk of TB transmission in households that implement adequate infection control measures, hospitalization for TB treatment is generally unwarranted (World Health Organization, 2009b). Thus, the WHO recommends that patients with drug-susceptible TB should be treated in home-based care, unless there are complications or comorbidities that necessitate hospital admission (World Health Organization, 2009b). Similarly, ambulatory-care models for MDR-TB are generally preferred to models of care that are based mainly on hospitalization (Falzon et al., 2011, Falzon et al., 2017). Decentralized care for MDR-TB provided by non-specialized providers and treatment supporters in local communities where patient reside has higher treatment success rate and reduced loss to follow up than centralized care for MDR-TB, which involves support by specialists providers and may include care at hospital outpatient clinics (Ho et al., 2017).

In both decentralized and centralized care, DOT is the standard practice, despite inconclusive evidence about the clear advantages of DOT over self-administered treatment (SAT) (World Health Organization, 2017c). Community or home-based DOT takes preeminence over hospital-based DOT, and trained providers administered DOT is superior to DOT provided by TB patient family members (World Health Organization, 2017c). In settings where technology and the requisite operational resources are available, video-observed treatment (VOT) is recommended as a potential replacement for DOT (World Health Organization, 2017c). Regardless, evidence from two cohort studies showed the lack of statistically significant difference between VOT and DOT, in terms of treatment completion and mortality (Chuck et al., 2016, Wade et al., 2012).

However, it is rationalized that VOT provides flexibility for TB patients daily schedule and facilitates adherence monitoring, especially when travel disrupts a planned DOT visit (World Health Organization, 2017c).

In the KSA guideline, individualized evaluation of TB patients for the choice of care model, whether hospitalization or ambulatory care, is mandatory. TB patients who are medically and mentally stable, having verifiable addresses and identification cards and are not residing in a congregate setting could be treated on ambulatory basis (Saudi Ministry of Health, 2014). By definition, "congregate settings include prisons, military barracks, refugee camps, homeless shelters, dormitories and nursing homes" (World Health Organization, 2009b).

It is uncertain whether mass gatherings, such as the Hajj constitutes a congregate setting. The KSA guidelines further recommend hospitalization after strict application of standard IPC measures in the following groups: critically ill TB patients, MDR-TB or XDR-TB patients, TB patients with comorbidity (HIV or uncontrolled diabetes) and those with history of non-compliance with TB treatment (Saudi Ministry of Health, 2014).

Safeguarding TB patients' access to palliative care alongside TB treatment alleviates suffering, especially for those with limited option for effective treatment, such as XDR-TB patients. The WHO recommends that the sufferings associated with TB should be tackled by providing accessible care services, ensuring adequate management of adverse events and addressing the psycho-social consequences of TB disease and its treatment, such as stigma and discrimination (World Health Organization, 2017a). Maintenance of IPC measures in the patients' residence, hospital and hospice is a necessary tool for end-of-life management of TB patients with exhausted treatment options to protect public health (World Health Organization, 2017a).

3.2.3 Conclusion

In conclusion, the KSA TB guideline largely evolved from the WHO TB treatment guidelines. Nonetheless, recent updates in the latter are not yet captured in published Saudi TB guideline. There is a need to update the national guideline based on current global TB management approaches, such as the withdrawal of CAT II regimen for TB retreatment and the phased introduction of Ultra for TB diagnosis. The diagnostic and treatment approaches for drug-resistant TB should be clearly addressed in the national guidelines to guide providers' treatment choices and to keep them regularly informed about latest evidence-based approaches, in this ever-evolving and vastly complex aspect of TB management and control.

3.3 Aims

The study overall aim was to document and asses the management of TB cases during the Hajj mass gathering and whether this follows current guidelines. The main objectives of the study were:

- To identify gaps and deficiencies in the management of TB cases during Hajj and areas for improvement.
- To assess whether the current national/international guidelines for TB management are suitable/appropriate for effectively managing TB cases in the unique and specific context of Hajj.
- To recommend best practices and public health policies for the optimal management of TB during the Hajj mass gathering which could also be beneficial to other mass gatherings worldwide.

3.4 Methods

3.4.1 Study design

A cross sectional study to document and assess the management of PTB cases during Hajj.

3.4.2 Study location

The study took place in Makkah, (KSA), the site of the Hajj pilgrimage. It comprised 13 hospitals situation in the city including Hajj holy sites, including temporary hospitals operational only during Hajj days, as shown in Table 2.

3.4.3 Study period

The study was conducted during the Hajj lunar month (1st-30thDulHija) during the 2016 and 2017 Hajj seasons, corresponding to 2nd September-1st October 2016 and 22nd August-21st September 2017, respectively.

3.4.4 Study population

The study enrolled hospitalized patients diagnosed with PTB during the study period under the below inclusion and exclusion criteria.

3.4.4.1 Eligibility criteria

Inclusion criteria

Inclusion criteria for the study were as follows:

- Consenting adults (>18 years old)
- Male and female
- Pilgrims or non-pilgrims
- Admitted to any of the selected hospitals during the study period and diagnosed with PTB

Exclusion criteria

Exclusion criteria from the study were as follows:

- <18 years of age
- Those who refuse to give consent for the study or consent could not be obtained
- Not diagnosed with PTB

3.4.5 Recruitment and data collection

3.4.5.1 Recruitment Process

Research assistants used hospital logbooks, admission information and information from the public health surveillance teams operational during Hajj to locate admitted patients with TB. The research team then approached the patients at an appropriate time to minimize any effect on patient care and obtained consent and enrolled the patients in the study. For severely ill patients, consent was obtained from eligible person and data was collected from the patient guardian/escort and other sources (e.g. clinicians and clinical records).

The management of TB patients in healthcare facilities during Hajj was documented using a specific data collection form (see Appendix 3: Data collection form for management of hospitalized patients with TB) and data was collected from patient's records, attending physician and through interviews with patients. Appropriate infection control measures using personal protective equipment (PPE) were used by researchers during visits to TB wards and during contact with hospitalized TB patients

3.4.5.2 Data collection tools

The data collection tools were carefully designed according to the study objectives and reviewed to ensure good understanding of questions and acquiring clear and precise answers. Questions were developed to be as precise and unambiguous as possible with emphasis on multiple choices and close-ended questions for accuracy. The study questionnaire and information sheet were translated to Arabic using a professional certified medical translator. Translated materials were then back-translated by someone else other than the first translator to make sure that the translation was as accurate as possible.

The study tools were tried and tested prior to the actual date of data collection in places different from the sample settings. Final versions of research tools were revised carefully. The researchers conducted all interviews in English, Arabic and other participant languages with assistance from the Mutawif to facilitate clear communication with pilgrims, especially non-literate pilgrims. The research team had training on good clinical practice and informed consent before starting data collection. The principal investigator also provided training on research methods to ensure that the study team understood the study collecting tools and research objectives. Clear step-by-step instructions regarding data collection was developed in English and Arabic and disseminated to the research assistants to maintain a standardized data collection process. PI and study team had determined the appropriate time to approach Mutawifs with medical missions' support. The study PI conducted training sessions (workshops) aimed to explain the aim of the study, objectives and Mutawifs' role during data collection as well as emphasised on patients' information confidentiality.

3.4.6 Data entry and cleaning

Data was entered following the gold standard for professional data entry which is double data entry. Data was entered twice in Excel and the two data sets were then compared, differences were examined, errors were verified against the original questionnaires and corrections were made. The data set was then exported to SPSS where frequencies for all variables were generated. The frequency tables generated were then examined to detect unusual values. Final database was cleaned by the principle investigator to ensure quality before analysis.

3.4.7 Data analysis

The survey questionnaire data was analyzed using SPSS 22.0 as the data management and analysis tool. Variables were characterized using frequencies and mean for the respective categorical and continuous variables. Then, a scoring system was developed, having identified four key themes from the questionnaire and literature review which were relevant to TB management in Hajj. The themes include identifying TB suspect, IPC and surveillance, diagnosing TB and treating TB. For each theme, we identified relevant indicators from the questionnaire that were related to the national guideline for TB management.

A score of 1 was assigned for each indicator/variable that was consistent with the 2014 KSA TB management guideline (latest version during study period) and 0 for inconsistency with the guideline. The indicator sub-score (x) for guideline consistency was obtained as follows:

X = Number of cases consistent with guidelines (c)/ Total number eligible of cases (d) * 10

The eligible cases summed the consistent and inconsistent responses with TB guideline and strictly excluded missing data and unknown responses. The guideline consistency score was obtained by calculating the mean of the indicator sub-scores for each theme.

3.4.8 Ethics

The study proposal was reviewed and approved by the King Fahd Medical City Internal Review Board (IRB log: 16-329E) (Appendix 5) and by LSTM REC approval (19-084). The study was conducted in accordance with the Ethics Committee's guidelines. Prior to enrolment in the study, potential participants were informed in detail about the protocol purpose and procedures and the risks and discomforts to be expected. Verbal consent was obtained from each participant and the person explaining and obtaining the consent signed and dated the data collection form. When a patient was illiterate or could not understand the consent statement due to language barrier, the consent statement was explained in his/her native language via Mutawif, the medical representative or a peer-pilgrim. The information sheet and informed consent statement were distributed to the participant to read and ask any questions and the content was explained to them. The participants were informed that they were free to withdraw their consent and to discontinue participation at any time without prejudice or loss of benefits to which they were otherwise entitled. The consent statement had the name and contact details of a study representative so that participants had the opportunity to ask further questions if they needed to.

3.4.9 Confidentiality

The importance of privacy and confidentiality of participants was highlighted to the study team. All relevant data and documents were secured in locked cabinets and/or password protected files; with access given to selected research personnel.

3.5 Results

The result of the study is discussed in several sections, depicting the main themes that were applied for assessing TB management in the Hajj. These include:

3.5.1 Sociodemographic characteristics of tuberculosis cases

Characteristics of the study population are presented in Table 17. For the two years period, 32 TB patients were recruited for the study from the included MOH hospitals serving pilgrims during the 2016 and 2017 Hajj seasons. Overall, 31 patients were being managed for drug-susceptible TB and 1 patient had XDR-TB. The mean age of the study population was 51.3 years (SD = 18.2 years, range 21-83 years). Most were males (25, 78.1%) and over half (17, 58.6%) were over 50 years old. However, 6 patients (20.7%) were in the age group 21-30 years. Few had higher education (10.0%) and over half (56.7%) had only primary or no formal education.

The TB patients were nationals of 10 countries (most from Saudi Arabia [34.4%] and the Philippines [12.5%]) but the majority (66.7%) had been residing in Saudi Arabia for at least one year (Table 17). Over one third of the TB confirmed cases (37.5%, 9/24) did not complete their Hajj rituals while the status of 50% of the cases (12/24) was not known. Three confirmed TB cases (12.5%) did complete their Hajj rituals in individual ambulances. For cases where the final outcome at the end of the study period was recorded (28 cases), 50% were discharged, 42.9% were still inpatients and 7.1% were referred. No mortality was recorded among the TB patients at the time when the study ended.

Table 17. Sociodemographic characteristics of the tuberculosis cases

Variable	Frequency n (%)
Gender	
Male	25 (78.1)
Female	7 (21.9)
Age group	
21-30	6 (20.7)
31-40	4 (13.8)
41-50	2 (6.9)
51-60	7 (24.1)
61-70	6 (20.7)
>70	4 (13.8)
Level of education	
No Formal Education	11 (36.7)
Primary Education	6 (20.0)
Secondary Education	10 (33.3)
University/Higher Education	3 (10.0)
Nationality	
Saudi Arabia	11 (34.4)
Philippine	4 (12.5)
Indonesia	2 (6.3)
India	3 (9.4)
Mali	2 (6.3)
Sudan	2 (6.3)
Somalia	2 (6.3)
Pakistan	3 (9.4)
Myanmar	2 (6.3)
Chad	1 (3.1)
Residence in the past year	
Saudi Arabia	18 (66.7)
India	3 (11.1)
Pakistan	1 (3.7)
Philippine	1(3.7)
Indonesia	1 (3.7)
Somalia	1 (3.7)
Chad	1 (3.7)
Myanmar	(3.7)

3.5.2 Tuberculosis risk factors patient characteristics

The proportion of drug-susceptible TB cases with potential or recognized TB risk factors was assessed in this study. These risk factors include history of recent travel to TB endemic countries, previous Hajj or Umrah performance, current and past tobacco smoking status and prevalence of chronic diseases among patients (Table 18).

The majority of respondents (21, 70%) reported they had not travelled outside their current residential areas in the previous 1 year. Only 25% (2/8) of respondents who reported prior travel visited high-burden countries (Pakistan and Indonesia). Regarding possible risk of TB exposure in a congregate setting, 69% (20/29) of respondents reported that they had not performed Hajj or Umrah within the past 1 year. The majority (75%, 6/8) of the previous Hajj or Umrah pilgrims were Saudi residents.

Tobacco smoking was not a predominant risk factor among drug-susceptible TB patients; the majority (72.2%, 21/29) indicated they were not current tobacco smokers. Only a small proportion (27.8%, 5/18) of the current non-smokers had prior history of smoking tobacco products. Unlike tobacco smoking, chronic diseases were highly prevalent among drug-susceptible TB patients. Nearly two-thirds of respondents (63.0%, 17/27) reported having various forms of existing chronic diseases, including diabetes (44.4%, 12/27), hypertension (25.9%, 7/27), cardiovascular diseases (14.8%, 4/27), chronic lung diseases (11.1%, 3/27) and chronic kidney disease (3.7%, 1/27).

Table 18. Results of risk factors characteristics of tuberculosis patients

Did you travel outside your current residential area in the past year?	
Yes	9 (30)
No	21 (70)
If yes, which country (s) did you visit?	
Saudi Arabia	5 (55.6)
Indonesia	1 (11.1)
Pakistan	1 (11.1)
Morocco	1 (11.1)
Sri Lanka	1 (11.1)
Have you performed Hajj or Umrah in the past year?	
Yes	8 (27.6)
No	20 (69.0)
Don't recall	1 (3.4)
Do you currently smoke any tobacco product?	
Yes	8 (27.6)
No	21 (72.2)
If no, did you ever smoke tobacco product in the past?	
Yes	5 (27.8)
No	13 (72.2)
Do you have any chronic health condition?	
Yes	17 (63.0)
No	10 (37.0)
If yes, do you have any of the following:	
Diabetes	
Yes	12 (44.4)
No	15 (55.6)
Chronic kidney disease	
Yes	1 (3.7)
No	26 (96.3)
Chronic lung disease	
Yes	3 (11.1)
No	24 (88.9)
Cardiovascular disease	
Yes	4 (14.8)
No	23 (85.2)
Hypertension	
Yes	7 (25.9)
No	20 74.1)

3.5.3 Infection prevention and control

Upon registration, most (76.6%, 23/30) suspected TB patients were admitted to an isolation room or ward. Otherwise, the patients were either admitted into the ER (6.7%, 2/30), ICU (6.7%, 2/30), neurosurgery ward (3.3%, 1/30), orthopedic ward (3.3%, 1/30) or general ward (3.3%, 1/30). While a proportion (48.4%, 15/32) of suspected TB patients was separated from other patients during registration, the triaging status of 45.2% (14/32) of suspected TB patients was not reported (Table 19). In a few instances (6.5%, 2/32), the suspected TB patients were not separated from other TB patients in the hospital.

While waiting diagnosis, most suspected TB patients (77.4%, 24/31) were housed in an isolation room or ward. Otherwise, the suspected TB patients were housed either in ER (12.9%, 4/31), ICU (3.2%, 1/31), neurosurgery ward (3.2%, 1/31), or general ward (3.2%, 1/31). On confirmation of drug-susceptible TB diagnosis, the proportion of TB cases isolated rose to 96.7% (30/31). Only 1 (3.2%) confirmed TB patient was managed in the ER. Generally, most (93.1%, 27/29) confirmed drug-susceptible TB patients spent less than 1 day in the health facilities before they were isolated. Delays in the isolation of confirmed drug-susceptible TB patient was documented in 2 cases, one 3-7 days and another over 7 days delay.

Table 19. Results of infection prevention and control tuberculosis management theme

Infection prevention and control	**Frequency n (%)**
Was the patient separated from other patients during registration (triaging)?	
Yes	15 (48.4)
No	2 (6.5)
Don't Know	14 (45.2)
Where was the TB suspected patient admitted while awaiting diagnosis?	
General Ward	1 (3.2)
ER	4 (12.9)
Isolation ward/room	24 (77.4)
ICU	1 (3.2)
Neurosurgery ward	1 (3.2)
Where was the confirmed PTB patient admitted in the healthcare facility?	
ER	1 (3.2)
Isolation ward/room	29 (93.5)
Neurosurgery isolation ward	1 (3.2)
How long was the confirmed PTB patient in the healthcare facility from arrival to isolation?	
<1 day	27 (93.1)
1-2 days	0 (0.0)
3-7days	1 (3.4)
>7days	1 (3.4)

TB=tuberculosis, PTB=pulmonary tuberculosis, ER=emergency room, ICU=intensive care unit

3.5.4 Early detection of drug-susceptible tuberculosis through systematic screening

This section focuses on the level of compliance with key recommendations for systematic screening of TB suspects to aid timely detection of TB cases (Table 20). In all cases, appropriate symptoms were sought from TB suspects. The most common symptoms obtained from TB suspects were cough ≥ 2 weeks duration (64.5%, 20/31) and fever with chills/ night sweat (67.7%, 21/31). Other TB symptoms were less frequently reported, and these include weight loss (32.3%, 10/31), any productive cough (22.6%, 7/31), chest pain (16.1%, 5/31) and hemoptysis (6.5%, 2/31).

The history of contact with active TB cases was obtained from 45.2% (14/31) of suspected TB cases. Nonetheless, the proportion of suspected TB cases for which providers did not obtain the history of contact with active TB cases was disproportionately lower (12.9%, 4/31), due to the large proportion of unknown responses (41.9%, 13/31) that were reported for this variable. In general, 44.8% (13/29) of the TB suspects were questioned about TB risk factors. Specifically, the proportion of TB suspects questioned about their country of residency, HIV status and potential occupational exposure to TB were 27.6% (8/29), 20.7% (6/29) and 27.6% (8/29) respectively. Furthermore, in the majority of case, providers used recommended screening test for active TB in case management; chest X- ray was conducted for 67.7% (21/31) of the TB suspects.

Table 20. Results for systematic screening of tuberculosis patients

Early TB detection through systematic screening	Frequency n (%)
Has the history of contact with active TB cases been obtained from suspected TB case?	
Yes	14 (45.2)
No	4 (12.9)
Don't Know	13 (41.9)
Has the suspected TB case been questioned about other TB risk factors?	
Yes	13 (44.8)
No	16 (55.2)
Was the suspected TB case asked about HIV status?	
Yes	6 (20.7)
No	23 (79.3)
Was the suspected TB case asked about occupational risk factors?	
Yes	8 (27.6)
No	21 (72.4)
Was the suspected TB case asked about its country of residence?	
Yes	8 (27.6)
No	21 (72.4)
What symptom warranted the suspicion of PTB?	
Cough ≥ 2 weeks	
Yes	20 (64.5)
No	11 (35.5)
Hemoptysis	
Yes	2 (6.5)
No	29 (93.5)
Any productive cough	
Yes	7 (22.6)
No	24 (77.4)
Chest pain	
Yes	5 (16.1)
No	26 (83.9)
Fever/Night sweats/chills	
Yes	21 (67.7)
No	10 (32.3)
Weight loss	

Cont..Table 20. Results for systematic screening of tuberculosis patients

Early TB detection through systematic screening	Frequency n (%)
Yes	10 (32.3)
No	21 (67.7)
Other symptoms	
Yes	9 (29.0)
No	22 (70.9)
Was an appropriate screening test for active TB conducted?	
Yes	21 (67.7)
No	10 (32.3)

TB= tuberculosis, PTB=pulmonary tuberculosis, HIV=human immunodeficiency virus

3.5.5 Diagnosing drug-susceptible tuberculosis

In terms of diagnostic period, 50% (5/10) of TB suspected patients within known health facilities visits status had > 2 visits to the health facilities before appropriate screening/diagnostic tests were ordered (Table 21). However, the period between patient registration/arrival in the health facilities and order of screening/diagnostic test was ≤12 hours in 77.4% (24/29) of cases. In nearly half (46.7%, 14/30) of the cases, the period between ordering screening/diagnostic tests and confirmation of TB diagnosis was 1-2 days. This diagnostic period was shorter (< 1 day) in 36.7% (11/30) and longer (3-7 days) in 16.7% (5/30) of cases. Using the difference between the date of confirmation of diagnosis and the arrival date as secondary proxy, the proportion of cases confirmed within each diagnostic period is given as: <1 day (16.6%, 4/24), 1 day (20.8%, 5/24), 2 days (25%, 6/24), 3 days (12.5%, 3/24), 4 days (12.5%, 3/24) and 5 days (8.3%, 2/24).

Sputum culture was the diagnostic test utilized in the majority (67.7%, 21/29) of cases. Smear microscopy alone and sputum culture combined with smear microscopy was used less frequently in 9.7% (3/29) and 19.4% (6/31) of cases respectively. Xpert MTB/RIF assay was not utilized for TB diagnosis. In one instance, none of the recommended diagnostic tests were ordered for the TB suspected patient. Only 12.9% (4/28) of suspected/confirmed TB cases were screened for HIV

Table 21. Results of variables related to tuberculosis diagnosis

Diagnosing TB	Frequency n (%)
Number of visits to the healthcare facility before screening/diagnosis tests were ordered for the patient	
1 visit	3 (30.0)
2 visits	2 (20.0)
>2 visits	5 (50.0)
Which diagnostic tests were ordered for the TB suspected patient?	
Sputum culture	21 (67.7)
Smear microscopy	3 (9.7)
Sputum culture + smear microscopy	6 (19.4)
None	1 (3.2)
Time between patient registration/arrival and the order of screening/diagnostic tests	
<1 hour	3 (9.7)
1-12 hours	21 (67.7)
>12-24 hours	2 (6.5)
>24 hours	3 (9.7)
Time between order of screening/diagnostic tests and confirmation of active PTB?	
<1 day	11 (36.7)
1-2 days	14 (46.7)
3-7 days	5 (16.7)
Was the suspected/confirmed TB patient screened for HIV?	
Yes	4 (12.9)
No	21 (87.1)

TB; tuberculosis, PTB, pulmonary tuberculosis, HIV; human immunodeficiency virus

3.5.6 Treating drug-susceptible tuberculosis

This section explores the compliance of providers with the requirements for drug-susceptible TB treatment, including the choice of an appropriate TB regimen. In over half of cases (58.1%, 18/31), the TB suspected patients were questioned about their previous TB treatment (Table 22). However, in quarter of the cases (25.8%, 8/31), it was not known if the previous history of TB treatment was obtained from the TB suspected patient. Regarding TB treatment regimen, the majority of confirmed TB patients (77.7%, 21/27) received either four 1st-line anti-TB drugs (INH-RIF-PZA-EMB) in 37.0% (10/27) of the cases or three 1st-line anti-TB drugs (40.7%, 11/27).

Among those that received three 1st-line anti-TB drugs, 54.5% received RIF-PZA-EMB, 36.6% had RIF-INH-EMB and 9.0 % were given INH-EMB-PZA. For the remaining patients, 11.1% (3/27) received two 1st-line anti-TB drugs (66.6% INH-RIF, 33.4% RIF-EMB), 7.4% (2/27) received one anti-TB drug (RIF) and one case was recorded to have received no anti-TB drugs. In general, RIF was the most subscribed anti-TB drug (in 25 cases), followed by EMB (in 22 cases) and INH and PZA (both in 17 cases).

Based on the duration of Hajj season (about one month), the possibility of monitoring treatment completion is unfeasible in a Hajj study. Thus, appropriate post-Hajj referral and provision of drugs to last during the referral period were proxies for estimating possible continuity of care. In most cases it was not known whether confirmed TB patients were referred for further treatment after completion of Hajj (77.3%, 17/22) or were given enough anti-TB drugs to last until they arrive in their country of residence (61.6%, 11/18).

Table 22. Results of variables related to tuberculosis treatment

Treating TB	**Frequency n (%)**
Has the TB suspected patient been questioned about his/her TB history? (i.e. previous TB diagnosis, previous TB treatment)	
Yes	18 (58.1)
No	5 (16.1)
Don't know	8 (25.8)
Was the confirmed PTB patient prescribed an appropriate treatment regimen?	
Four 1st-line agents	10 (37.0)
Three 1st-line agents	11 (40.7)
Two 1st-line agents	3 (11.1)
One 1st-line agents	2 (7.4)
None	1 (3.7)
Was the confirmed PTB patient given enough TB treatment to last until his arrival to his/her country of origin?	
Yes	6 (33.3)
No	1 (5.6)
Don't know	11 (61.1)
Was the confirmed PTB patient referred for further treatment after Hajj?	
Yes	1 (4.5)
No	4 (18.2)
Don't know	17 (77.3)

3.5.7 Tuberculosis case notification

This section focuses on the compliance of providers with the mandatory requirement for notification of TB cases. In 76.7% (23/30) of cases, the confirmed TB cases were reported to the KSA MOH preventive medicine department (Table 23). The reporting status of 23.3% (7/30) of the TB patients was unknown. A proportion (44.8%, 13/29) of the confirmed TB cases was reported to the appropriate country medical missions' office. This excludes the 48% (14/29) of confirmed TB cases with unknown medical missions' reporting status. Among the latter, 57.1% were Saudi residents. The study also showed that the confirmed TB case status of two residents of Pakistan and Myanmar were not reported to their respective country medical mission's office.

Table 23. Results of tuberculosis notification variables

Notification	Frequency n (%)
Was the confirmed PTB patient reported to his country's medical office?	
Yes	13 (44.8)
No	2 (6.9)
Don't know	14 (48.3)
Was the confirmed PTB patient reported to the Ministry of Health preventative medicine department?	
Yes	23 (76.7)
Don't know	7 (23.3)

PTB=pulmonary tuberculosis

3.5.8 Guideline compliance scores

As illustrated in Figure 19, out of a maximum possible score of 10, the guideline compliance score was highest for the themes IPC and surveillance (9.6) and identifying TB suspects (7.2). The least scores were obtained for the themes treating TB (5.0) and diagnosing TB (3.0). Tables 24-27 show how these scores were calculated and the contribution of variables to their respective final theme score is depicted as sub-scores in Figure20.

For identifying TB suspects, a maximum compliance sub-score (10) was obtained for "implementing symptom-based screening". Lower but above average sub-scores were recorded for "obtaining relevant history of TB close-contact" (7.8) and "conducting appropriate TB screening tests" (6.8). The least sub-score (4.5) was obtained for "obtaining history of TB risk factors". A maximum sub-score (10) were also obtained for "pre-diagnosis admission ward" and case notification, under the IPC and surveillance theme. Slightly lesser sub-scores were calculated for other variables, including "post-diagnosis admission ward" (9.7) and "triage management" (8.8).

For diagnosing TB, the sub-score for "number of diagnostic visit" was 5.0. In comparison, the sub-scores obtained for "appropriate diagnostic tests" and "HIV testing" were 2.9 and 1.3 respectively. These latter sub-scores further downgraded the total theme score for diagnosing TB. Similarly, the sub-scores of two variables further reduced the final theme score for treating TB (Figure20). Despite scoring 7.5 for "pre-diagnosis treatment", the sub-scores for "appropriate TB regimen" (3.1) and "transfer out" (2.0) reduced the final theme score for treating TB to less than average.

Table 24. Calculating guideline consistency score for identifying tuberculosis suspects theme

Indicator	KSA TB management guideline	Total eligible cases[1] (d)	Number of cases consistent with guideline (c)	Indicator score (x)
Symptoms and signs was basis for screening suspected TB case?	Persons with signs and symptoms consistent with TB should be evaluated for TB	31	31	31/31*10 X =10
TB suspect questioned about history of close contact active PTB cases?	All close contacts of patients with PTB should be screened for TB	18	14	14/18*10 X =7.77
TB suspect questioned about TB risk factors?	Systematic screening of high risk groups, especially people living with HIV and workers exposed to silica for active TB	29	13	13/29*10 X =4.48
Which screening tests were ordered for the TB suspected patient?	Chest radiography is recommended as a non-diagnostic screening test for active PTB	31	21	21/31*10 X =6.77
Guideline compliance score				29.02/4 =7.25

[1]=Excludes missing data and unknown response

KSA; Kingdom of Saudi Arabia, TB; tuberculosis, PTB, pulmonary tuberculosis, HIV; human immunodeficiency virus

Table 25. Calculating guideline consistency score for infection prevention and control and surveillance theme

Indicator	KSA TB management guideline	Total eligible cases[1] (d)	Number of cases consistent with guideline (c)	Indicator score (x)
TB patient separated from other patients in the healthcare facility during registration (triaging)	people suspected of having TB must be separated from other patients, placed in adequately ventilated areas	17	15	15/17*10 X =8.82
Where the TB suspected patient admitted while awaiting diagnosis	TB suspects should not be admitted to wards harboring severely immunocompromised patients	31	31	31/31*10 X =10
Where the confirmed PTB patient admitted in the healthcare facility?	In case of hospitalization, TB patients should be admitted into TB wards	31	30	30/31*10 X =9.67
Confirmed PTB patient reported to the Ministry of Health preventative medicine department	All providers must report TB cases and their outcomes to appropriate local authorities in line with local policies and laws	23	23	23/23*10 X =10
Total guideline consistency score				38.49/4 =9.62

[1]=Excludes missing data and unknown responses

KSA; Kingdom of Saudi Arabia, TB; tuberculosis, PTB; pulmonary tuberculosis

Table 26. Calculating guideline consistency score for diagnosing tuberculosis theme

Indicator	KSA TB management guideline	Total eligible cases[1] (d)	Number of cases consistent with guideline (c)	Indicator score x
1. Appropriate diagnostic tests were ordered for the TB suspected patient	• Sputum microscopy should follow chest radiographic findings consistent with TB	31	9	9/31*10 **X =2.90**
2. Was the new TB patient screened for HIV	• Test all TB patients for HIV before starting TB treatment	31	4	4/31*10 **X =1.29**
3. ≤ 2 visits before TB diagnosis was confirmed	• Examine two consecutive smears over 2 days (including 1 early morning sample)	10	5	5/10*10 **X =5.0**
Total guideline consistency score				9.19/3*10 =**3.06**

[1]=Excludes missing data and unknown response

KSA=Kingdom of Saudi Arabia, TB=tuberculosis, PTB=pulmonary tuberculosis, HIV=human immunodeficiency virus

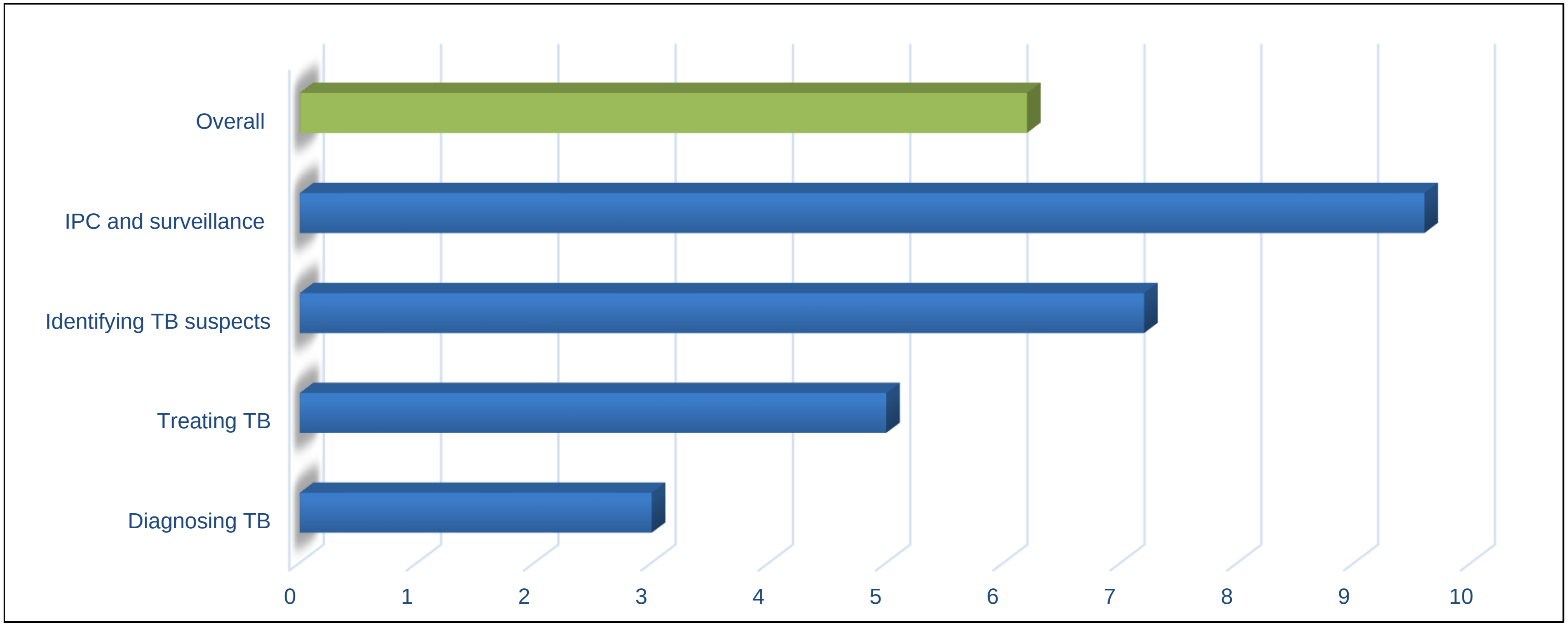
Table 27. Calculating guideline consistency score for the treating drug-susceptible tuberculosis theme

Indicator	KSA TB management guideline	Total eligible cases[1] (d)	Number of cases consistent with guidelines (c)	Indicator score x
1. Patient received potential 1st-line or 2nd-line agents before confirmation of PTB?	• TB treatment must not be started before confirmation of TB diagnosis	18	17	17/18*10 **X =9.44**
2. Was the confirmed PTB patient prescribed an appropriate treatment regimen	• 2INH-RIF-PZA-EMB/4INH-RIF implies use of 4 drugs in the intensive phase and 2 drugs in the continuation phase	27	10	10/27*10 **X =3.70**
3. Was the confirmed PTB patient referred for further treatment after Hajj?	• -Optimal daily dosing required throughout treatment • -Linkage to continuous care (transfer-out) is vital for preventing treatment interruption	5	1	1/5*10 **X =2.0**
Total guideline compliance score				15.1/3 **=5.04**

[1]=Excludes missing data and unknown response

KSA=Kingdom of Saudi Arabia, TB=tuberculosis, PTB=pulmonary tuberculosis, INH=isoniazid, EMB=ethambutol, PZA=pyrazinamide

Figure 19. Chart showing tuberculosis guidelines compliance scores (out of 10) for tuberculosis management



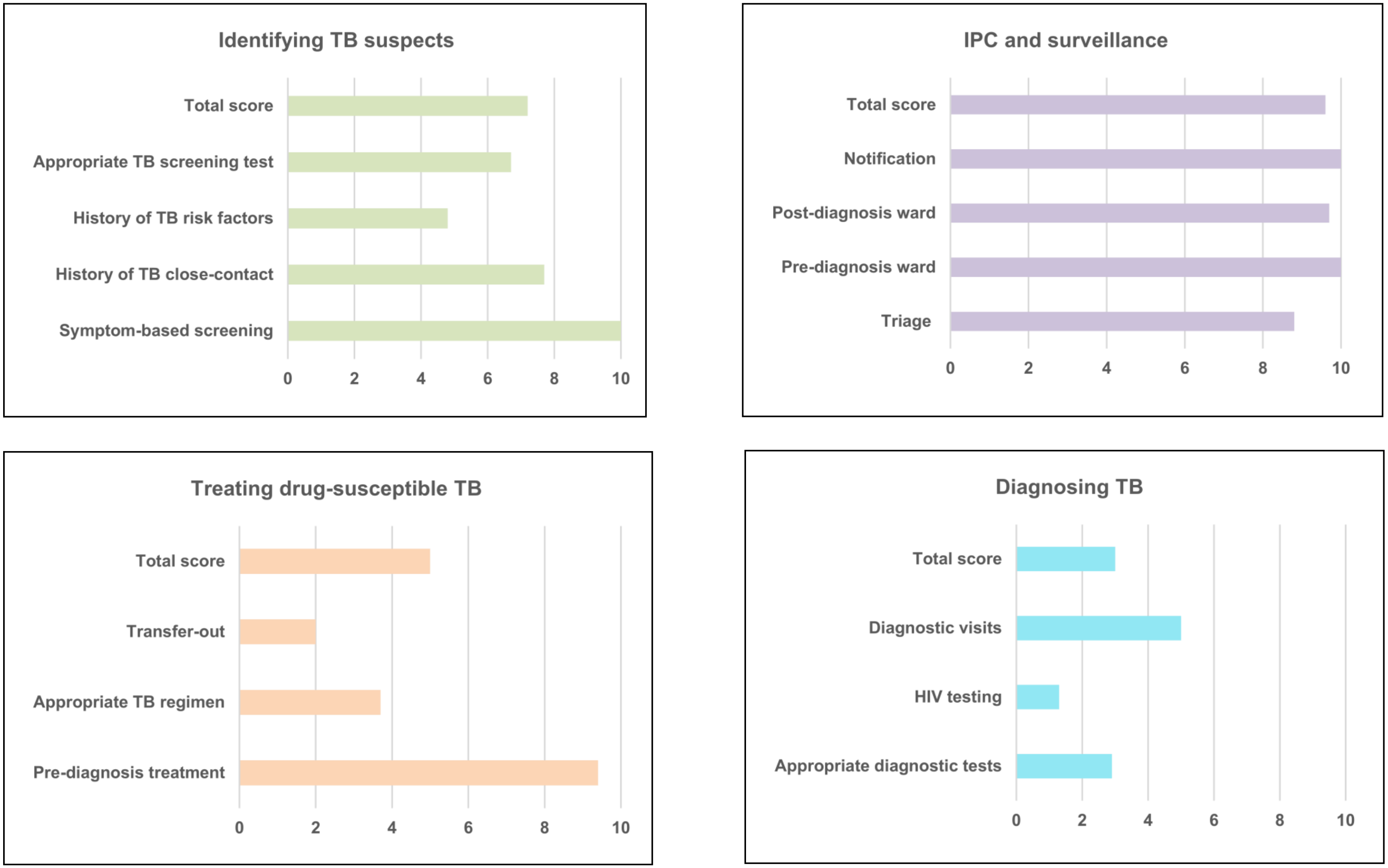


Figure 20. Shows sub-scores (out of 10) for each main theme describing the level of compliance with tuberculosis guideline

3.5.9 Managing extensively drug-resistant tuberculosis

The management approaches for the single case of XDR-TB is discussed in this section.
The confirmed XDR-TB patient was a 32-year-old female Philippine national, who has been residing in Saudi Arabia for at least the previous 1 year. She had only primary education and did not work in fields of increased occupational exposure or risk of TB. She was known to be diabetic and had no recent history of travel from her country of residence in the previous year. She had not performed Hajj or Umrah in the past and had no current or prior history of tobacco smoking. It was unknown whether providers obtained relevant history of TB risk factors, including HIV status, from the patient.

The patient presented to the healthcare facility on the 18th of August 2016 and on arrival, providers separated her from other patient based on her presenting signs and symptom (chest pain). She was initially admitted in the ER with an admission diagnosis of community acquired pneumonia. The case was confirmed to have TB on the same day of arrival at the healthcare facility and was transferred to an isolation room where she remained until discharge. The records showed that the TB screening and diagnostic tests carried out for the patient were chest X-ray and sputum culture. Other vital investigations for TB such as smear microscopy and HIV testing were not ordered for the patient. The patient was questioned regarding previous TB treatment and defaulting from it, but it was not reported if she was questioned regarding relapse after previous TB treatment. The case was confirmed as XDR-TB on the 5th September 2016, 18 days after admission and isolation.

The confirmed XDR-TB patient was notified to the MOH's preventive health department, as well as her medical officer. The patient was treated and discharged but it was not known if she was discharged to complete her Hajj rites, or whether she was referred after Hajj or given sufficient treatment for the transit period. It was also unclear, if she was commenced on a recommended regimen for XDR-TB

3.6 Discussion

This study exemplifies the compliance of tertiary healthcare providers with national guidelines for TB management. The result showed high level of compliance with the assessed indices for systematic screening of TB suspects, IPC and case notification, but low compliance scores were obtained for prompt TB diagnosis and use of standardized treatment regimen for drug susceptible TB.

Most TB cases in the current study were males (78.1%) which is in accordance with global data. The WHO estimates that in 2016, among the 10.4 million people who fell ill with TB, 65% were males (World Health Organization, 2017b). Data from national TB surveys from numerous countries indicate higher burden of TB disease among males with the male to female ratios of cases ranging from 1.2 (in Ethiopia) to 4.5 (in Vietnam) for bacteriologically confirmed TB. In most countries, the ratio was in the range 2-4(World Health Organization, 2017b). Over half of the TB cases were over 50 years old (58.6%) with primary or no formal education (56.7%). Extremes of age are risk factors for TB,(Marais et al., 2013) and the prevalence of TB increases with age (Hoa et al., 2010, Onozaki et al., 2015, Qadeer et al., 2016). Similarly, TB risk, prevalence and impact are 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 (Jurcev-Savicevic et al., 2013, Needham et al., 2001, Sanchez-Barriga, 2015). Studies conducted among Hajj pilgrims also found supportive results. For instance, Alzeer and colleagues (Alzeer et al., 1998) reported that the mean age of TB patients during the 1994 Hajj was 60 years, while in 2015, Yezli et al.(Yezli et al., 2017b) found that the age of undiagnosed TB cases among pilgrims was 58.5 years. In the latter study, pilgrims aged over 64 years were 5.3 times more likely to be TB positive than those aged 47 years old or less. Also, education was strongly associated with TB prevalence and pilgrims with no formal education being 4 times more likely to have TB (Yezli et al., 2017b).

Beside the predominant older males distribution of cases, socio-demographic risk factors for TB, such as history of tobacco smoking, visit to, or residence in high-burden countries and occupational exposure were uncommon among TB patients in the study. Yezli and colleagues (Yezli et al., 2017b) reported that the prevalence of undiagnosed TB in Hajj was higher among pilgrims residing in South Asia and those who traveled outside their current country of residency in the previous year, although the association was not statistically significant for these factors. Among the TB cases identified, 80% were from Afghanistan 13.3% from Pakistan and 6.7% from Nigeria. Also, 26.6% of the cases reported traveling to a TB endemic country in the previous year. It is known that travel to TB-endemic areas is a risk for TB (Marais et al., 2013).

In our study, around 28% of the TB cases reported being current smokers and a similar proportion indicated that they did smoke in the past. This is higher than that reported in another study among Hajj pilgrims with TB (13.3%) (Yezli et al., 2017b) but lower than figures from international reports (Brunet et al., 2011, Kolappan and Gopi, 2002, Mahishale et al., 2015). There is strong evidence that smoking is significantly associated with increased risks of TB infection and disease, TB mortality and recurrent TB (Bates et al., 2007, Khan et al., 2015, Kolappan and Gopi, 2002, Lin et al., 2007). Also TB patients who have smoked are more likely to transmit TB to their contacts (Kenyon and Zondo, 2011). In addition, exposure to environmental tobacco smoke and passive smoking increases the risks of TB infection and developing disease (du Preez et al., 2011, Lin et al., 2007, Sridhar et al., 2014). 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 sever progression to TB (Altet-Gomez et al., 2005, Leung et al., 2015). Smokers develop more extensive pulmonary disease, more lung capitation and cavitary lesions, more positive sputum smear and culture at the baseline and are more likely to require hospitalization (Altet-Gomez et al., 2005, Leung et al., 2015). It is estimated that by 2050, smoking would lead to an excess of 18 million TB cases (Loddenkemper et al., 2016).

Previous Hajj or Umrah performance were uncommon among TB patients in this study. While these events are not an established risk factor for TB transmission, few studies have shown that clinically-recognized or undiagnosed active TB are potential sources of TB transmission during these mass gatherings (Alzeer et al., 1998, Wilder-Smith et al., 2005, Yezli et al., 2017b). Pilgrims were reported to have a 10% risk of acquiring TB infection after attending the Hajj (Wilder-Smith et al., 2005). Given the overcrowded living conditions of pilgrims, which are similar to the situation in highlighted congregate settings for TB transmission (prisons, refugee camps etc.), Hajj or Umrah performance may have far-reaching implications in the global epidemiology of TB.

The majority (66.7%) of TB patients in this study were KSA residents. This may be explained by the fact that the study included both pilgrims and non-pilgrims and that healthcare facilities in Makkah provide healthcare to pilgrim and non-pilgrim during the Hajj. Although Saudi Arabia is not a high TB burden country, TB incidence in the country show significant regional variation with the Makkah region showing much higher TB incidence rates than the rest of the country and rising trend (Al-Orainey et al., 2013, Yezli and Memish, 2012). In addition to the hosting of the Hajj and Umrah mass gatherings, this high TB incidence may also be related to the fact that 40% of the Makkah region population are non-Saudis, many originate from and frequently visit high TB burden countries (Al-Orainey et al., 2013, Yezli and Memish, 2012). Some of this population are illegal immigrants who also tend to live in poor housing conditions and have limited access to healthcare because of fear of deportation. It is likely that they contribute significantly to the high incidence of the disease in the Makkah region (Al-Orainey et al., 2013). Regardless, it is evident that previously postulated control measures for TB, such as pre-arrival screening for active TB should not only target international pilgrims or those arriving from high burden countries (Yezli et al., 2017b), it should also identify effective strategies for systematic/targeted screening of intending pilgrims from within the Kingdom.

Beyond socio-demographic risk factors, 63% of the TB patients in this study reported they had coexisting chronic diseases. This includes 44.4% of TB patients that had diabetes. This is higher than that reported internationally (Bates et al., 2012, Hochberg et al., 2017, Peltzer, 2018). The presence of chronic diseases, especially immunosuppressive health conditions, increases the risk of TB disease, predisposes to severe illness and complicates TB treatment (Falzon et al., 2011, Stevenson et al., 2007).

In a study among Hajj pilgrims, at least 33% of TB cases had an underlying health condition, mainly diabetes or hypertension and although not statistically significant, pilgrims with underlying health conditions were twice more likely to have TB than those without an underlying health condition (Yezli et al., 2017b). Bates and colleagues (Bates et al., 2012) reported the co-morbidity of diabetes, respiratory, renal and cardiovascular disorders with culture-positive TB in inpatients to be 21.1%, 15.5%, 10.5% and 3.2% respectively. The burden of TB was significantly greater in diabetes patients (OR =6.6, p= 0.025). As such, the management of co-morbidities is now a key focus of the integrated, patient-centered care and prevention strategy of global TB control (World Health Organization, 2015a).

Generally, home-based care for TB is preferred to methods of care that are based on strict hospitalization (Saudi Ministry of Health, 2014, World Health Organization, 2016e). In the KSA context, medical or mental instability and residence in congregate settings are among factors that may warrant hospitalization (Saudi Ministry of Health, 2014). In this study, most of the suspected and confirmed TB patients were admitted and isolated for TB management. To the best of our knowledge, there is no standardized global protocol guiding the choice of suitable models of care-whether home based or hospitalized care- during international mass gatherings. However, considering the constant mobility of pilgrims and challenges in verifiable or stable residences for pilgrims during Hajj, hospitalization, although undesirable, seems a logical and practical choice for TB management during the mass gathering. Nonetheless the psycho-social consequences of prolonged isolation could be exacerbated among TB patients that are unable to or hindered from performing their Hajj rites due to hospitalization. In addition to the psycho-social needs of TB patients, hospitalization fuels the nosocomial transmission of TB especially in resource-limited settings lacking adequate IPC measures (Escombe et al., 2010, Kanjee et al., 2011).

IPC in healthcare settings is one of the key strategies for TB control (World Health Organization, 2009b). However, implementation of IPC recommendations seems to be inadequate with several studies reporting poor TB infection control measures in health facilities (Demissie Gizaw et al., 2015, Farley et al., 2012, He et al., 2010, Ogbonnaya et al., 2011). Further, many HCWs are practicing without adequate infection control training and often lack knowledge on TB infection control strategies (Demissie Gizaw et al., 2015, Kanjee et al., 2011, Shrestha et al., 2017, Woith et al., 2012).

In the current study, we report high compliance with the aspects of TB IPC measures investigated, with a combined compliance score for IPC and surveillance of 9.6 out of a maximum score of 10. Effective separation of patients presenting with symptoms and signs consistent with TB (Triage) was reported in nearly half of cases though the triage management of a similar proportion of patients was unknown. The result also showed that the majority (76.6%) of TB suspects were admitted in an isolation ward or room, while awaiting TB diagnosis. On confirmation of TB diagnosis, all but 2 patients were admitted in negative pressure isolation rooms for TB management.

The high compliance scores for IPC may stem from measures taken by the KSA MOH to prevent and control the recent national healthcare-related outbreaks (not Hajj-related) of Middle East Respiratory Syndrome (MERS) in some major cities in the Kingdom (Rabaan, 2017) MERS causes acute respiratory distress syndrome and while its precise mode of transmission is still unclear, like TB, it does spreads through infected person's respiratory secretions such as through coughing and sneezing (Xiao et al., 2018). Thus, the infection control practices for TB and MERS are comparable and targeting one disease may have dual impact on both diseases control efforts. The implementation of standard TB infection control practices is often challenging in low-income countries, due to the high cost of achieving and maintaining the requisite standards. In such settings, TB infection control is undermined by inadequate staff training, lack of infection control policy and unavailability of effective screening procedures and suitable isolation areas for suspected TB patients (Escombe et al., 2010, Kanjee et al., 2011). Since a proportion of these low-income countries send pilgrims to the Hajj and set up clinics to provide health services for their pilgrims, the aforementioned factors may also impact on TB control during the pilgrimage, especially if these largely temporary health facilities are poorly monitored and regulated by the KSA MOH.

In the current study, providers utilized presenting symptoms to correctly identify suspected TB patients in all cases. Cough and fever with chills/night sweat were the most frequent symptoms among patients. This finding corroborates existing evidence that identifies cough as the most common symptom of PTB (Santha et al., 2005, World Health Organization, 2011a, 2013c). Adequate knowledge of TB symptoms and risk factors among providers are prerequisites for correct and prompt identification of suspected TB patients for screening and diagnosis (Saudi Ministry of Health, 2014, World Health Organization, 2017a).

In such regards, we found that less than half of the TB suspected cases were questioned about TB risk factors. In majority of cases (67.7%), chest X-ray, a recommended screening tool for active TB, was conducted for the TB suspects. Chest X-ray is particularly more sensitive for TB screening after a positive symptom screening (Van't Hoog et al., 2013, World Health Organization, 2013c). In view of the significant use of both symptom-based and radiological screening methods in this study, a total guideline compliance score of 7.2 out of 10 was obtained for the prompt identification and screening of TB suspects theme for TB management.

A low guideline compliance score was obtained for the TB diagnosis theme with reference to national and international diagnostic standards. Sputum culture was the only recommended diagnostic test applied in about 70% of cases. Since TB testing using sputum culture takes at least 2-3 weeks to produce results, the application of sputum culture as the singular diagnostic test is not consistent with approved standards for TB diagnosis. By the third day of arrival in the health facility, 79.1% of the suspected TB cases had been confirmed to have drug-susceptible TB. Apparently, while still waiting for sputum culture results, providers relied on screening tests, such as chest X-ray for the confirmation of TB diagnosis. This practice is inconsistent with both national and international guidelines; chest radiography is only recommended for screening purposes.

The 2014 KSA TB guidelines recommended that appropriate sputum samples should be obtained for microscopy from all suspected TB patients following chest radiology or symptom-based screening (Saudi Ministry of Health, 2014). The guideline further recommended the use of Xpert MTB/RIF as an initial diagnostic test for all suspected TB patients, on a conditional basis(Saudi Ministry of Health, 2014). As such, the latter was not included in the scoring criteria for this study; scoring was premised on the inclusion of sputum microscopy in the diagnostic cascade for TB. Nonetheless, Xpert MTB/RIF, which could detect TB and MDR-TB by proxy in the same da y(World Health Organization, 2010b), was not applied for TB diagnosis in this study.

This is potentially related to lack of knowledge regarding this recent technology and lack of Xpert MTB/RIF testing capability in many settings across the Kingdom. Although available in a number of Saudi hospitals, the roll out of Xpert MTB/RIF has been slow, and the application of the molecular testing method is mainly confined to reference laboratories for diagnosis and research but not for point-of-care testing (Somily et al., 2016, Yezli et al., 2017b).

Understandably, KSA is not among the countries with high-burden of TB globally and there are other competing national public health priorities (World Health Organization, 2017b) However given that the Kingdom regularly hosts pilgrims from several countries, including high-burden countries, the Hajj and Umrah-related prevalence and epidemiology of TB may differ from those of the entire country. Evidently, Kingdom-wide, TB infection is more prevalent in the Hajj and Umrah host cities (Jeddah, Makkah and Medina) (Yezli and Memish, 2012). In addition to the epidemiological considerations, access to same day diagnosis of TB could prove valuable in a highly mobile Hajj population where follow-up visits to the same health facility may not be guaranteed. For example, the observed prolonged delay in the confirmation of the only MDR-TB case in the current study could have been avoided if Xpert MTB/RIF testing was available and used. As such, KSA authorities should consider the provision of Xpert MTB/RIF testing capability in health facilities within the Hajj areas to facilitate rapid (same day) diagnosis of TB during the mass gatherings, in line with national and international TB control goals.

The risk of developing TB is estimated to be 20 (17-23) times greater in people living with HIV than among those without HIV infection and TB is the leading cause of death among people with HIV (World Health Organization, 2017d). In 2017, an estimated 920,000 people living with HIV worldwide fell ill with TB and 300,000 people died from HIV-associated TB in the same year (World Health Organization, 2017b, 2017d). Due to the synergistic relationship between HIV and TB, it is recommended that all TB patients should be screened for HIV (World Health Organization, 2017a). Yet, only a fraction of TB patients were questioned about their HIV status (20.7%) or tested for HIV (12.9%) in this study. This is much lower than what is reported globally. According to the WHO, 60% of new and relapse TB patients (3.8 million) in 2017 had a documented HIV test (World Health Organization, 2017d). As a low prevalence setting, knowledge of HIV among healthcare workers is low in Saudi Arabia (Memish et al., 2015b).

On the other hand, in high HIV/TB prevalence countries such as South Africa, it was reported that 94% of healthcare workers screen TB patients for HIV (Bhebhe et al., 2014). Considerably, HIV could be a more frequent comorbidity among pilgrims who arrive with active TB from areas with high HIV disease prevalence (World Health Organization, 2017b).

More so, a missed or delayed HIV diagnosis in a TB patient stalls the commencement of appropriate treatment and results in poor outcomes for the patient, community and health system (Yan et al., 2015). Therefore, healthcare providers in KSA ought to be trained and guided to conduct screening for HIV and other comorbidities in all suspected TB patients irrespective of their nationality.

The main strategies to control TB are early diagnosis and prompt treatment initiation. Delayed diagnosis of TB can enhance the transmission of infection, worsen the disease, increase the risk of death, and may be a reason why TB incidence has not declined substantially, despite the global scale-up of DOTS (Dye and Williams, 2010, Golub et al., 2006, Pablos-Mendez et al., 1996). Several reasons for delays have been identified and have typically been attributed to either patients or the health system (Finnie et al., 2011, Rossato Silva et al., 2012, Sreeramareddy et al., 2009). Patients not seeking medical care in a timely fashion cause patient-related delay. Health-system delays are primarily due to healthcare professionals not considering TB at the point of care. Reports have implicated inexperience diagnosing and treating TB as a reason for missed opportunities to diagnose TB (Chen et al., 2010, Golub et al., 2005). Studies have also reported poor knowledge and practices in relation to TB diagnosis among healthcare workers including physicians (Wahab et al., 2016). In the current study, 50% of TB cases had more than 2 visits to healthcare facilities before TB screening/diagnosis tests were ordered for the patients. Other studies also reported such findings. One US study found that within 30 days before an initial TB diagnosis, 15.9% of patients (25.7% for 90 days) had a respiratory-related hospitalization or emergency department visit (Miller et al., 2015). Over half of the 5795 initial TB diagnoses had at least one previous visit to healthcare facility without a TB diagnosis. In a systematic review on delays in diagnosis and treatment of PTB in India, about 48% of all patients first consulted private providers and 2.7 healthcare providers, on average, were consulted before diagnosis (Sreeramareddy et al., 2009). Yet, our results are concerning, as delays in diagnosing TB during Hajj may lead to significant transmission given the crowded setting during the event.

As such, because of delays in diagnosis and failure to utilize the appropriate diagnostic tests for suspect TB patients, the combined score for the TB diagnosis theme was 3 out of a maximum of 10, the lowest score of all TB management themes in the current study.

Both the KSA and WHO guidelines for TB management recommend the use of four 1st-line anti-TB drugs (INH, RIF, PZA and EMB) in the treatment of drug-susceptible TB (Saudi Ministry of Health, 2014, World Health Organization, 2017a). The guideline compliance score for TB treatment in this study was 5 out of 10; partly because the majority (63%) of TB patients received fewer than four 1st-line anti-TB drugs. A significant proportion (40.7%) of the TB patients received three 1st-line anti-TB drugs, mostly in regimens containing RIF-PZA-EMB and INH-RIF-EMB. This finding is consistent with the result of a Spanish study which showed that 44.3% of TB patients received three 1st-line anti-TB drugs in the intensive phase of TB treatment (Garcia-Garcia et al., 2016). The rate of inadequate TB drug regimen prescribing was 73% in another study that assessed the compliance of doctors with TB management guidelines in China (Zheng et al., 2014). In general, inappropriate treatment of TB is common worldwide. In a systematic review, Langendam et al. (Langendam et al., 2012) assessed the percentage of TB patients that received an inappropriate treatment regimen (type, dose, frequency of dosing and combination) from 37 studies from 22 countries, and one study was from multiple countries. Almost all continents were represented. Inappropriate treatment regimens were prescribed in 67% of the studies and the percentage of patients on inappropriate regimens varied between 0.4% and 100%. Poor knowledge of national and international TB management guidelines contributes to inappropriate prescription of anti-TB drugs by healthcare providers, and the use of inappropriate regimen drives the occurrence of relapse and the emergence of drug-resistant TB (Fox et al., 1999, Hoffman et al., 2016, van der Werf et al., 2012, World Health Organization, 2014a).

Indeed, one case of XDR-TB was observed in this study. An estimated 6.2 % of MDR-TB patients have XDR-TB and many remain undetected due to unavailability of requisite laboratory capacity for drug-resistant TB diagnosis (World Health Organization, 2017b). The singular XDR-TB patient was known to have diabetes and had been on TB treatment before admission. Diabetes is a known risk factor for XDR-TB (World Health Organization, 2014a).

The patient was diagnosed with TB and isolated on the same day of arrival to the healthcare facility which potentially reduced the risk of nosocomial transmission of primary XDR-TB infection. However, there was a prolonged delay before the case was confirmed as XDR-TB.

It is unclear whether this delay had an impact on the treatment or outcome of the case. In general, while individuals with MDR-TB with a prolonged delay to treatment are perceived as more likely to have a higher bacillary burden, more extensive lung damage and, as a result, active TB disease that is harder to treat, little evidence is available to support these assumptions (Harris R. C. et al., 2016). Nevertheless, rapid diagnosis of MDR- and XDR-TB is crucial to reduce the risk of transmission, especially in congregated settings and crowded environments such as the Hajj. Access to rapid molecular point of care testing is needed in KSA and the Hajj to speed up MDR/XDR-TB diagnosis and ensure the immediate isolation of MDR/XDR-TB patients to prevent community and healthcare-related transmission of the primary MDR/XDR form of the TB bacilli.

Notification of all confirmed TB cases is mandatory under national and international TB regulations. All confirmed TB cases with known notification status were reported to the Saudi health authorities, including the XDR-TB case. However, 2 cases of TB, involving international pilgrims were not notified to their country health representatives during Hajj. Without adequate proof of notification, it is unknown whether the continuum of care was maintained for the two international pilgrims who had to return to their home countries soon after the pilgrimage (before the end of the treatment period). Any travel-related treatment interruptions could breed treatment relapse and drug-resistance and propagate community spread of TB. Perhaps there is no formal mechanism for reporting of notifiable diseases to the country health missions/representatives. The existing notification framework mandates country health missions/representatives to report cases of certain notifiable diseases encountered in their country health facilities to the Saudi health authorities (Alotaibi et al., 2017). Even so, the compliance with the notification protocol has been variable and occasionally low.

Both national and international TB guidelines fall short of providing guidance on TB control at international mass gatherings, including procedures for ensuring access to care and support services during travel. Thus, the development and dissemination of a multi-national Hajj and Umrah-specific TB protocol is needed to provide guidance on: TB case notification, IPC, screening and diagnostic methods, TB treatment regimen and models of care. The protocol should include pathways for the safe transfer across borders and follow up of TB patients involved in the mass gatherings.

3.7 Study strengths and limitations

The current study is among the foremost surveys of TB management at international mass gatherings. While the small number of cases and high proportion of unknown responses for some variables constituted limitations, the TB management indices obtained was a fair representation of the compliance of providers with national and international TB guidelines in MOH hospitals during the Hajj.

3.8 Summary

In summary, the study investigated for the first time the management of TB cases in MOH hospitals serving pilgrims during the Hajj mass gathering. Data was collected from 31 TB cases during the 2016 and 2017 Hajj seasons. Out of a maximum guideline compliance score of 10 for the selected TB management themes, scores were highest for IPC and surveillance (9.6) and identifying TB suspects (7.2). The least scores were obtained for treating TB (5.0) and diagnosing TB (3.0). These findings provides a basis for the review of existing practices across settings-private and public sector vs national and foreign health facilities- and serves as a reference for the development of appropriate guideline and protocol for TB management at the Hajj and Umrah, as well as other settings with similar health system resources and population dynamics hosting recurrent international mass gatherings.

Chapter 4: Tuberculosis knowledge, attitude and practice among healthcare workers during the 2016 hajj mass gathering

4.1 Executive summary

TB is a global health issue with significant morbidity and mortality. Knowledge deficiencies and poor attitude and practices of HCWs related to TB can have a detrimental impact not only themselves and their individual patients, but also the global population as a whole.

Annually, over 2 million pilgrims attend the Hajj religious mass gathering in Saudi Arabia. The latter, ensures healthcare for pilgrims through numerous health facilities across the holy cities of Makkah and Madinah that are fully equipped and staffed by 1000s HCWs drafted from across the Kingdom. We investigated KAP of HCWs deployed in Hajj in relation to TB and its management.

A KAP survey was conducted among 540 HCWs from 13 hospitals serving pilgrims during the 2016 Hajj. HCWs originated from 17 different countries and included physicians, nurses as well as other HCWs. Nearly half of the participants declared dealing with TB patients during their day-to-day work. In general, we report that HCWs had average knowledge (mean knowledge score of 52%), above average attitude (mean attitude score of 73%) and good practice (mean practice score of 81%) regarding TB, based on our scoring system and cut-off points.

Knowledge gaps were identified in relation to the definition of MDR-/XDR-TB and LTBI, smear microscopy results, length of standard TB treatment for drug-sensitive TB, 2nd-line anti-TB drugs, BCG vaccination, and appropriate PPE to be used with active PTB patients. Poor attitudes were found in relation to willingness to work in TB clinic/ward and to the management and treatment of TB patients. In addition, HCWs were not aware of the actual risk of TB infection connected with their work. Poor practices were reported for commencing anti-TB treatment on suspected TB cases before laboratory confirmation and in increasing natural ventilation in TB patients' rooms.

There was a statistically significant difference in knowledge scores in relation to age, gender, nationality, level of education, occupation and length of work experience as well as a significant difference in practice scores in relation to the level of education. There was a weak but statistically significant positive correlation between knowledge and attitude and between attitude and practice.

Given the context of Hajj, the potential global health consequences of mismanagement of TB cases at the event and the results of the current study, we recommend the following:

- HCWs should receive tailored, high quality, periodic TB education and training including before deployment to Hajj with ongoing monitoring and evaluation of the impact. Training should be determined according to job categories, needs, and educational backgrounds.
- Training should not only emphasise the theoretical aspects of training but also skill-based components to impact on practice. Various means shown affective in bringing about behavioral change among HCWs should be used including traditional and non-traditional methods of communicating information.
- HCWs should be encouraged to keep up-to-date with recent scientific literature and advances in TB management and control as well as being aware of national and international guidelines and best practices.
- Special attention should also be given to addressing factors beyond training (e.g. lifestyle, health system, job satisfaction as well as Hajj-related factors) that could influence HCWs' KAP regarding TB, so as not to reinforce the limitations and weaknesses of current practices.

4.2 Introduction and literature review

A search of electronic databases was conducted for relevant literature in English, without time restriction. Database searched included Pubmed, Scopus and Google Scholar. A combination of the MeSH terms and text words including: "Tuberculosis", "TB", "Pulmonary", "Occupation", "Risk", "Latent", "Prevention", "Knowledge", "Attitude", "Practice", "Healthcare workers" were used. A manual search was also performed reviewing reference lists of identified literature to find additional papers. With few exceptions, only the most relevant and recent publications were used to develop the literature review.

4.2.1 Tuberculosis and occupation

Tuberculosis (TB) is a treatable, communicable disease that has two general states: latent infection and active disease. With few exceptions, only those who develop active TB in the lungs or larynx can infect others, usually by coughing, sneezing, or otherwise expelling tiny infectious particles that are inhaled by others (Institute of Medicine, 2001). TB is not only a public health concern but also an occupational health concern as it can be directly related to work. Rodriguez Bayarri and Madrid San Martin(Rodriguez Bayarri and Madrid San Martin, 2004) noted that most adults work as part of a team rather than in isolation, spending on average 1,540 hours a year together. Given the mode of transmission of TB, potential TB contacts and infections may occur at the workplace. The risk of infection is dependent on the potential of coming in contact with the bacillus and may include a number of factors such as the prevalence of TB in the community and the population of workers, the number of workers who come into contact with TB cases, the type of work undertaken, the virulence and infectious dose emitted by the person with TB, as well as susceptibility of the host to infection (Institute of Medicine, 2001, Rodriguez Bayarri and Madrid San Martin, 2004). The risk of contact with and contracting TB is particularly high in certain settings such as in healthcare facilities, geriatric facilities, homeless shelters, and prisons (Institute of Medicine, 2001).

TB infection has been linked to various occupations and increased incidence of TB has been observed in particular types of jobs which are invariably associated with an elevated risk of TB including impoverished and unskilled workers, occupations which increase susceptibility to the infectious organism, such as in mining and pottery work, and occupations which may increase the likelihood of exposure to transmission.

The latter includes working in acute care hospitals, extended care facilities, and mycobacteriology laboratories (Institute of Medicine, 2001, Usui et al., 2000). Snider(Snider, 1991) classified the professions or occupations carrying risk of TB into 3 categories (Table 28). The first category included occupations, and therefore workers, who are more affected by TB, usually for sociocultural reasons. Categories 2 and 3 relate to occupations where there is a possibility of TB infection that occurs when work material or workplace procedure are able to actively transmit pathogens or passively provoke susceptibility to the disease in workers who are performing their normal duties (Rodriguez Bayarri and Madrid San Martin, 2004, Snider, 1991). Rodriguez Bayarri and Madrid San Martin(Rodriguez Bayarri and Madrid San Martin, 2004) further explored these categories (Table 28). They noted the 3 categories as: category 1; nonoccupational TB with no causal relationship to the workplace, which comprise those in workers of a similar sociocultural status, for example immigrants or unskilled workers, who congregate in the same jobs and workplaces, and therefore face a higher risk of contagion among themselves because of a coincidental occupational relationship. Category 2; occupational TB with a direct passive causal relationship considered intrinsic to the workplace. This category include work that involve increase susceptibility to TB due to silicosis and pneumoconiosis related to inhalation of free silica dust and exposure to asbestos and other organic and non-organic dusts (Davies, 2001, Horai, 1975, Rees and Murray, 2007); Category 3; occupational TB with an active intrinsic causal relationship to the workplace resulting from the work material or workplace procedure being the source or origin of the bacilli causing the disease. Examples of such occupations include healthcare workers (HCWs), laboratory workers, and those working in facilities housing people with high prevalence of TB such as workers with refugees and asylum seekers, prison inmates and immigrants (Institute of Medicine, 2001, Rodriguez Bayarri and Madrid San Martin, 2004).

4.2.2 Tuberculosis and the risk for healthcare workers: a historical prospective

Although TB is a well-established occupational risk for HCWs and the concern about the threat of TB to HCWs is considered long-standing, the certainty and unanimity on the idea that care of patients with TB represents a risk to HCWs is in fact relatively recent. Sepkowitz (Sepkowitz, 1994) reviewed the medical literature from the 1900s onwards and noted that a combination of genuine confusion, ignorance, and willful neglect conspired to keep the debate on the risk of TB to HCWs active and unsettled as late as the 1950s.

He highlighted a number of factors that contributed to the delay in recognizing TB as a risk for HCWs including liability concerns, loss of patronage for private hospitals, the fear of scaring young woman away from nursing as well as some experts simply believing that the higher incidence of TB among HCWs was a results of increased surveillance in this population compared to the general public and not evidence of increased risk (Sepkowitz, 1994). The debate moved from TB being considered not a risk for HCWs to a recognition of increased risk of primary TB infection among HCWs but not of disabling TB, to the current understanding that TB infection in all its forms is an occupational hazard for HCWs (Baussano et al., 2011, Kilinc et al., 2002, Nasreen et al., 2016, Seidler et al., 2005, Sepkowitz, 1994).

Early literature on the subject not only reported that TB was not a health risk for HCWs but that caring for TB patients conferred a health advantage to the care provider (Sepkowitz, 1994). The latter notions were supported by a number of early studies and observations in the field. In studies conducted in 1882 and 1909, Williams, of the Brompton Hospital for Consumption in London, UK, reported that of hundreds of workers at Brompton who had cared for thousands of cases of TB, none had developed TB (Williams, 1882, 1909). A similar claim was noted in 1930 by Baldwin, Director of the Trudeau Foundation, New York, USA, who stated that no case of pulmonary TB has been known to develop among hundreds of healthy employees at the Trudeau Sanitorium during 45 years (Baldwin, 1930). Other studies in the early 1900s of more than 18,000 sanatoriums workers in Europe (Sepkowitz, 1994) further reinforced the widely held view in the medical world at the time that TB work involved no special hazard among those engaged in it (Dublin, 1914).

In the 1920s however, the results of several studies conducted at a time where the prevalence of TB among young adults was much lower than that of previous generations, begin to determine objectively the risk to HCWs including nurses and doctors (Sepkowitz, 1994). The risk of TB infection among nurses was first to be recognized starting by landmark series of articles from Oslo by Heimbeck (Heimbeck, 1928, 1936). In 1924, Heimbeck reported that among the 220 tuberculin negative nursing students at time of entry to nursing school, 210 (95%) had converted by the time they graduated. Moreover, 48 (22%) cases of TB occurred in this group compared with 3 (1.5%) among 200 initially tuberculin-positive nurses (Heimbeck, 1928).

Further studies in the 1930s and 1940s in nursing schools, sanatoria, and other medical facilities reported rate of tuberculin conversion above that expected in the general population, and many found an increase in cases of TB especially among those initially turbeculin-negative (Sepkowitz, 1994). Reported tuberculin conversion rates among nurses ranged between 79 and 100% with cases of TB found in 2-12% of the study population (Sepkowitz, 1994). One study concluded that nurses were 500 times more likely than the general public to develop TB (Boynton, 1939). Moreover, results of a survey that reported on 10,000 HCWs, as well as on 20,000 additional cases reported in the literature, found that TB was 3 times more likely in initially tuberculin-negative persons compared with those who were initially tuberculin-positive (Daniels, 1944, Daniels et al., 1948). The latter findings led to a recommendation from many experts that “tuberculin-negative nurses should not work in the TB wards" (Daniels et al., 1948).

Similar to nurses, risk to medical students, physicians and other HCWs was also recognized relatively recently with mounting evidence from studies reporting conversion rates or rates of active TB among this group of HCWs in the early and mid1900s. For instance, Abruzzi (Abruzzi and Hummel, 1953) used data from 42,000 persons who were medical students from 1940 to 1950 to calculate a rate of active TB of 334/100,000 per year which was 3 to 10 times higher than that in the general population in the 1940 (Rose, 1953). Mikol et al. (Mikol et al., 1952) determined the relative risk of TB according to hospital occupation and found that persons with direct patient contact, such as nurses and technical workers, were 8 to 10 times more likely to develop TB than those at the same institution who did not have patient contact. However, even with such evidence, many still argues that although primary TB infection was occurring at alarming rates among HCWs, these primary infections did not translate into active disabling TB and the rates of active TB or mortality from TB among this population was not different from that in the community. For instance, Amberson and Riggins (Amberson and Riggins, 1936) noted that their TB ward at the Bellevue Hospital, New York, USA, had over 3,100 patients between 1931 and 1936, cared for by over 1,000 nurses. While most of the initially tuberculin-negative nurses did convert, they reported that only 8 out of 539 (1.5%) of nurses developed active TB during the study period (6 of these cases were mild), an attack rate similar to that to be expected in the general community according to the authors.

This view appeared to be backed by early reports on mortality rates due to TB among HCWs, which showed that few physicians died of TB compared to men in other occupations (Sepkowitz, 1994). For instance, physicals had a TB date rate of 23.7/100,000, close to that of bankers, brokers and lawyers (18.3-19.3/100.000) but much lower than that of coal mine operatives, waiters and factory and construction laborers (106/100,000, 180/100,000 and 227.3/100,000 respectively) (Brandy, 1940, Sepkowitz, 1994).

It was only in the 1950s that the medical community finally agreed that a significant occupational risk existed with regards to HCWs and TB. As the incidence of TB declined in the later years, so did the concern about TB as an occupational hazard for HCWs (Sepkowitz, 1994). However, poor implementation of infection control measures, the effect of the human immunodeficiency virus (HIV) epidemic on TB, and the emergence of multidrug-resistant (MDR) strains which resulted in the re-emergence of nosocomial transmission of TB and MDR-TB in the 1980s and 1990s, including numerous outbreaks and TB-related deaths among HCWs, led to the issue of TB and HCWs' safety being once again of the highest importance in recent years (Sepkowitz, 1994, von Delft et al., 2015).

4.2.3 Tuberculosis and the risk for healthcare workers

4.2.3.1 Infection, active disease and mortality

TB has long been recognised as an important occupational hazard for HCWs, although medical consensus on the topic was only achieved in the 1950s in resource-rich countries (Sepkowitz, 1994). The risk of exposure to infectious TB in healthcare settings is generally expected to be higher than that in the community and TB has been reported as the most common occupational infectious diseases among HCWs in a number of countries (Ahn and Lim, 2008, Malangu and Legothoane, 2012). However, based on surveillance data and studies' findings in different healthcare settings, this issue remains heated in controversies (Tam and Leung, 2006). This is mainly due to the fact that outcomes of studies reporting risk of TB infection, disease and mortality among HCWs differ depending on numerous factors. These include pre- vs post-chemotherapy ears and outbreak vs non-outbreak settings. For example, Menzies et al. (Menzies et al., 1995) reviewed the risks of TB infection and disease among HCWs reported in the medical literature, as well as risk factors found for single case transmission and prolonged hospital TB outbreaks.

They reported a significantly increased risk of TB was found in the pre-chemotherapy era. However, in the post-chemotherapy era, the risk ratios ranged from 0.6 to 2.0, with the highest risk occurring among those whose occupations involved the preparation of histological specimens and involvement with autopsy procedures. In outbreak reports included in the review, the percentages of exposed HCWs being infected ranged from 14 to 55%, whilst the percentages of those developing active disease ranged from 2.2 to 8.4%. Some of the factors reported to have contributed to the outbreaks were delay in diagnosis, poor infection prevention and control practices, jet irrigation of thigh abscess, and autopsy procedures (Menzies et al., 1995). Tam and Leung (Tam and Leung, 2006) noted however, that there were a number of important limitations to the studies included in the review, including lack of age adjustment, healthy worker effect, possible misclassification of occupation, recall bias, and low response rates in some of the questionnaire studies.

Another important consideration is the actual contribution of community vs occupational exposure to TB among HCWs and risk attributable to nosocomial transmission as well as the incidence of the disease in the general population. Nardell and Sepkowitz (Nardell and Sepkowitz, 2004) reported that in the USA community-based exposure predominated before 1985 as studies from the period showed that the HCW tuberculin conversion rate was related to socio-economic status or place of residence rather than the job categories. During the period 1985 to 1992, occupational risk was reported mainly in outbreak settings related to HIV infection or MDR-TB which demonstrated that jobs with higher TB exposure risks were associated with tuberculin conversion (Greenaway et al., 2002, Louther et al., 1997). Lack of evidence for occupational risk outside the outbreaks settings in the USA, led the Centers for Disease Control and Prevention (CDC) and others to conclude that outside outbreak settings, community exposure was the dominant risk factor for tuberculin test conversion in the USA HCWs and that the occupational risk to HCWs of TB infection is close to that in their community of residence (Institute of Medicine, 2001, Nardell and Sepkowitz, 2004).

However, given that the USA is a high-income country, the CDC's conclusions may not be applicable to countries with limited resources. In a review of the risk of TB infection and disease among HCWs , Menzies et al. (Menzies et al., 2007) reported on studies published between 1950 and 2005 for low- and middle income countries and studies post 1995 for high-income countries.

They found that the median annual incidence of TB infection attributable to healthcare work was 5.8% ranging from 0 to 11% in low- and middle-income countries and 1.1%, ranging from 0.2 to 12% in high-income countries. The observed differences probably reflected the availability of resources and infection control measures in healthcare settings. Other reports from both high and low- middle income countries found that 32 to 80% of TB cases among HCWs were work-related (Fica et al., 2008, Nienhaus, 2009).

In a recent review, Baussano et al. (Baussano et al., 2011) demonstrated that the risk for TB among HCWs was consistently higher than the risk among the general population worldwide, confirming that TB is an occupational disease. They also reported that in low, intermediate and high TB incidence countries, 49%, 27% and 81% of TB cases respectively, among HCWs were attributable to exposure in the healthcare settings.

In addition to the above, a number of other factors have been reported in the literature to impact the risk of TB infection and diseases among HCWs. These include: 1). Factors related to the patients' population and the management of TB patients, the prevalence of TB among the patient's population, the number of TB patients examined, the number of patients with unrecognized TB, delays in diagnosing TB, number of patients with MDR-TB and those receiving inappropriate treatment, have all been reported to be risk factors (Alele et al., 2018, Baussano et al., 2011, Fica et al., 2008, von Delft et al., 2015) 2).

Factors related to the HCWs' age, gender, duration of employment as well as their individual susceptibility/immune status. (Alele et al., 2018, Fica et al., 2008, Malangu and Legothoane, 2012, von Delft et al., 2015) 3). Factors related to healthcare settings, access to appropriate ventilations systems, and adequacy of infection prevention and control measures. These include poor ventilation without negative pressure in isolation rooms or not keeping the doors closed, high levels of air recirculation, inadequate use of masks by HCWs, noncompliance with aerosol dissemination precautions such as during mechanical ventilation, bronchoscopy, dress change, jet irrigation of thigh abscess, and autopsy procedures (Alele et al., 2018, Baussano et al., 2011, Fica et al., 2008, Menzies et al., 1995, von Delft et al., 2015) 4).

Certain clinical procedures increase the risk of infection from clinical contacts. For example, procedures that provoke cough to induce sputum, therapeutic tracheobronchial intubations, anesthetic intubations, intubations for examination or simple cleaning of the upper airways, bronchoscopies, lung function tests, or the administration of curative or preventive pharmacological aerosols (Menzies et al., 1995, Rodriguez Bayarri and Madrid San Martin, 2004) In addition, other procedures undertaken during laboratory work and autopsies such as the use of electric saws or pneumatic aspirators-injectors during autopsies and shaking or stirring of clinical samples in laboratories, also increase the risk of transmission (Rodriguez Bayarri and Madrid San Martin, 2004). As such, certain types of occupations and wards, or work locations have been linked to increased risk of TB. These include hospital employees in wards with TB patients, chest disease wards, emergency rooms; nurses in hospitals; nurses attending HIV-positive or drug-addicted patients; pathology and laboratory workers; respiratory therapists and physiotherapists; physicians in internal medicine, anaesthesia, surgery and psychiatry; paramedics and non-medical hospital personnel in housekeeping and transport work (Fica et al., 2008, Joshi et al., 2006, Kilinc et al., 2002, Seidler et al., 2005, von Delft et al., 2015).

4.2.3.2 Tuberculosis infection (Latent tuberculosis)

HCWs are at increased risk of being exposed to and acquiring TB than the general population especially in high-burden countries (Nasreen et al., 2016). HCWs may develop active TB and become an important source of TB infection to others in both healthcare and community settings. However, HCWs may also be infected without showing signs of TB or being infectious, termed latent TB infection (LTBI). While LTBI does not produce disease manifestations and is not infectious, it does result in persistent immune response against *Mycobacterium tuberculosis* antigens. There is also a 10–15% life-time risk of developing active TB. Several factors increase the risk of progressing from infection to active TB, including HIV infection or immunosuppressive treatment, malnutrition, diabetes and alcohol abuse as well as being infected within previous 2 years (Getahun et al., 2015, Jensen et al., 2005). Therefore, preventing active TB by addressing these risk factors as well as proper diagnosis and treatment of LTBI in selected risk groups such as HCWs is important for the individual and for public health (Jensen et al., 2005).

According to the WHO, in countries with a low TB incidence, systematic testing and treatment for LTBI may be considered for HCWs (Jensen et al., 2005). Periodic screening of HCWs in considered an important component of TB programs in many countries according to the background TB incidence in the population. In fact, serial testing for TB among HCWs seems to be more appropriate in order to identify recent infections and to target infected individuals for preventive therapy (Pai et al., 2014).

There is no gold standard test for diagnosis of LTBI. Tuberculin skin test (TST) and blood interferon-gamma release assay (IGRA) tests (especially Quantiferon, QFT) are performed to diagnose LTBI (Lamberti et al., 2015). However, these tests are limited in their ability to distinguish latent infection from cured or treated infections and to predict progression to active TB (Trajman et al., 2013). Other limitations including TST's reduced sensitivity due to malnutrition, severe TB diseases and immunodeficiency, TST's decreased specificity in settings where non-tuberculous mycobacteria are prevalent and in populations who have received the Bacillus Calmette-Guérin (BCG) vaccine post-infancy or via multiple vaccinations as well as frequent reversion and conversion reported from serial testing by IGRA rendering interpretation difficult (Lamberti et al., 2015, Trajman et al., 2013). In addition to their limitations, it appears that the results of these tests are not always in agreement. Lamberti et al.

(Lamberti et al., 2015) conducted a recent systematic review and meta-analysis of 29 studies and found that the Cohen's k for agreement between TST and QFT for 24 of them was 0.28 (95% CI: 0.22-0.35), with the best value being in high TB burden countries and lowest rate of BCG vaccination. They concluded that "currently, there is no gold standard for TB screening and the most-used diagnostic tools show low agreement. For evidence-based health surveillance in HCWs, occupational physicians need to consider a number of factors influencing screening results, such as TB incidence, vaccination status, age and working seniority" (Lamberti et al., 2015). Nevertheless, TST remains the major tool used around the world for diagnosis of LTBI because of well-established algorithms for test interpretation and cost-effectiveness.

A number of studies reported the prevalence of LTBI or incidence of LTBI (conversion rate) among HCWs dating back to the early 1900s. Investigations among nurses in the USA between 1924 and 1943 reported that over half had LTBI with the prevalence of TST-positive results ranging between 48 and 59% (Sepkowitz, 1994). The incidence of LTBI were high with the majority of TST-negative nurses seroconverting by the end of the study periods (TST conversion rates ranged between 79 and 100%). Studies conducted during TB outbreaks in the 1970s reported TST concession rates among HCWs of 31-35% (Craven et al., 1975, Ehrenkranz and Kicklighter, 1972). The USA CDC investigated a number of hospital outbreaks in the early 1990s and reported TST conversion rates ranging from 33 to 50% (Sepkowitz, 1994). In recent years, there have been a number of reviews in relation to the risk of TB among HCWs reporting prevalence and incidence of LTBI (Table 29, Table 30). The reported rates differed depending on a number of factors including the countries income and TB endemicity, the characteristics of the HCWs population studies (age, gender, level of education, BCG vaccination, length of employment, job characteristics and location), study setting, study date and duration, the type and characteristics of test used to determine LTBI, and infection prevention and control measures at the study sites.

In 2005, Seidler et al. (Seidler et al., 2005) systematically reviewed reports on LTBI among HCWs included studies from low incidence, high income countries the USA, Spain, Canada, Germany, Australia and UK during 1971–1999 and found prevalence of LTBI ranging from 5% to 55% in different occupations. They also reported that the annual risk of TB ranged from 0.1 to 1.2% (Seidler et al., 2005). In 2006, Joshi et al (Joshi et al., 2006) reported on the incidence and prevalence of LTBI among HCWs in low- and middle-income countries including Uganda, India, Brazil, Iran, Ivory Coast, Turkey, Mexico, Thailand, Peru, Trinidad and South Africa. The prevalence of LTBI among HCWs was, on average, 54% (range 33-79%). The prevalence of LTBI among nurses, a subgroup with high level patient contact, ranged from 43 to 87%. The review also reported the prevalence of LTBI among medical and nursing students which was found to vary widely between studies from 2 to 40% with an overall pooled prevalence of 12%(Joshi et al., 2006). BCG vaccination rates ranged between 66 and 100% for medical and nursing students and 33 and 79% for all HCWs. The estimates of annual risk of LTBI (tuberculin conversion) ranged from 0.5 to 14.3%, after accounting for the incidence of TB infection in the general population, and the risk attributable to occupational exposure ranged from 2.6% to 11.3%.

Another review in 2007 summarized data from studies published between 1950 and 2005 from low- and middle-income countries and 1990 and 2005 from high-income countries. The median prevalence of LTBI in HCWs was 63% (range 33–79%) in low- and middle-income countries and 24% in high-income countries (range 4–46%). BCG vaccination was mostly above 60% for HCWs from low- and middle-income countries and ranged between 0 and 89% for studies from high- income countries. Among HCWs from low- and middle-income countries, LTBI was consistently associated with markers of occupational exposure, but in high-income countries it was more often associated with non-occupational factors (Menzies et al., 2007). The median annual risk of TB infection in low- and middle-income countries was estimated at 5.3%, ranging from 0.5 to 14.3%. Incidence estimates were lower in studies that recruited young medical and nursing students. After accounting for the incidence of TB infection in the population, the risk attributable to occupational exposure ranged from 0 to 11.3%, with a median of 5.8%. For high-income countries, the median annual risk of TB infection was lower, 1.1% (range 0.2-12). The risk attributable to occupational exposure ranged from 0.1 to 11.8% (Menzies et al., 2007).

A systematic review and meta-analysis published in 2011 included studies from previously published reviews (Joshi et al., 2006, Menzies et al., 1995, Menzies et al., 2007) and additional studies published during between 2005 and 2010 worldwide (Baussano et al., 2011). The stratified pooled estimates for the LTBI rate for countries with low (<50 cases/100,000 population), intermediate (50–100 cases/100,000 population), and high (>100 cases/100,000 population) TB incidence were 3.8% (95% CI: 3.0%–4.6%), 6.9% (95% CI 3.4%–10.3%), and 8.4% (95% CI: 2.7%–14.0%), respectively. The stratified pooled annual risk of LTBI estimates were 3.8% (95% CI: 3.0%–4.6%), 6.9% (95% CI: 3.4%–10.3%), and 8.4% (95% CI: 2.7%–14.0%), respectively. Given that most studies in the meta-analysis were from countries with low TB incidence and that the variability of estimates was higher from countries with intermediate and high TB incidence, the overall pooled estimates of annual risk of LTBI was 4.6% (95% CI: 4.1%–5.6%) (Baussano et al., 2011). A 2016 review and meta-analysis investigated literature published between 2005 and 2015 on the prevalence of LTBI among HCWs from 7 high-burden countries (Bangladesh, Brazil, China, India, South Africa, Uganda, and Zimbabwe)(Nasreen et al., 2016).

The prevalence of LTBI ranged from 6.9% among medical students to 97.6% among all types of HCWs. The pooled prevalence among all HCWs and among medical and nursing students was 47% (95% CI: 34%-60%,) and 26% (95% CI: 6%-46%) respectively. Incidence of LTBI was available for HCWs in Brazil, China, South Africa and Zimbabwe. The cumulative incidence ranged from as low as 2.8% among Brazilian medical students to as high as 38% among all types of HCWs in South Africa (Nasreen et al., 2016).

Few studies reported on LTBI among HCWs in Saudi Arabia in general or among those working during the Hajj. A population based study in Saudi Arabia conducted between 2010 and 2013 found that the prevalence of LTBI among 1,369 subjects from the general population was 9.1% using the Quantiferon-TB gold in tube (QFT-GIT) test and 9.3% using TST (Balkhy et al., 2017). Abbas et al. (Abbas et al., 2010) investigated the prevalence of LTBI among newly hired HCWs in 4 major tertiary care hospitals in Riyadh city in KSA. Of the 2,650 HCWs surveyed between 2008 and 2009, 291 (11%) were positive for TST with the highest rates among physicians (14.9%) nurses (12.9%) and those aged 50 years or older (32.6%). El-Helaly and colleagues (El-Helaly et al., 2014) conducted a retrospective cross-sectional study among 1,412 HCWs screened for LTBI between 2009 and 2011 at a tertiary care hospital in Riyadh. The majority of the HCWs (92.6%) had received BCG vaccination. LTBI prevalence was 29.8% and 23.6% using the TST and the QFT-GIT test respectively. Similar results were also reported from another tertiary care center in Riyadh among 1,595 HCWs, most of whom (90.6%) had BCG vaccination. TST positivity was observed in 31.5% of the HCWs while QFT-GIT test was positive in 25%(Al Hajoj et al., 2016). Balkhy et al. (Balkhy et al., 2014) investigated HCWs who were exposed to patients with TB at medical city in Riyadh. Of the 298 HCWs identified most were female (62.9%), non-Saudi (83.9%), nurses (68.6%), and working in critical care locations (72.8%). The prevalence of LTBI at start of the employment was 51.2% (63/123). Of the 115 exposed HCWs who had negative or unknown pre-exposure TST status 53 (46.1%) were positive after exposure and were diagnosed with post-exposure LTBI. Although most were prescribed and started LTBI therapy, 82.6% of those starting therapy failed to complete the recommended course.

Only one study specifically investigated the prevalence of LTBI among HCWs working during Hajj. In 2015, Bukhary et al. (Bukhary et al., 2018) screened 520 HCWs working at multiple secondary care hospitals in the Hajj pilgrimage region for LTBI using QFT-GIT. They included HCWs who had previously worked in the Hajj and who had no close contact with pulmonary TB patients within the previous 3 months or recent history of a positive TST. Over half of the HCWs were males (66.9%) and non-Saudi (57.5%) and most (98.5%) had BCG vaccination. Nearly 40% had contact with TB patients more than 4 months prior to participating in the study and 8.5% were TST positive. Of the 520 HCWs enrolled 50% were clinical staff involved with direct patient care including nurses (30.8%) and physician (19.2%). The prevalence of LTBI was 10.8% and was significantly higher in physicians, in HCWs working at chest hospitals and those with longer employment duration.

4.2.3.3 Developing tuberculosis

In addition to the risk of infection, HCWs are at risk of developing TB disease (Table 31). There is historical evidence of documented increased risk of TB disease among HCWs. For instance, one study from 1939 concluded that nurses were 500 times more likely than the general public to develop TB (Boynton, 1939).

Another report from the 1950s found that medical students had 3 to 10 times higher rates of TB disease than that in the general population (Abruzzi and Hummel, 1953, Rose, 1953).Even in recent years, TB may be responsible for up to 5 additional cases of TB per 100,000 individuals among HCWs in relation to the general population in developing countries (Fica et al., 2008). Seidler et al.(Seidler et al., 2005) reported that the overall incidence of TB disease among native-borne HCWs in high-income countries was 25/100,000 per year compared to 10/100,000 per year in the general population.

Data from low- and middle-income countries found higher rates with annual incidence of TB disease among HCWs ranging from 69 to 5,780/100,000 with an attributable risk of TB disease in HCWs, compared with the general population, ranging from 25 to 5,361/100,000 per year (Joshi et al., 2006). HCWs in facilities with fewer HCWs for every TB patient seen (HCW-to-patient ratio less than 50/100 TB patients), had a higher incidence of TB disease. Baussano et al. (Baussano et al., 2011) reviewed TB among HCWs from countries with low, intermediate and high TB incidence.

They reported that the median estimated annual incidence of TB among HCWs was 67/100,000 (Inter quartile range; IQR 40–142), 91/100,000 (IQR 81–723) and 1,180/100,000 (IQR 91–3,222) for studies from countries with low, intermediate, and high TB incidence, respectively. These estimates where higher than those estimated for the general population from countries in all three categories (33/100,000 (IQR 27–37), 82/100,000 (IQR 58–223), and 311/100,000 (IQR 168–405), respectively). Median estimated annual TB incidence rate ratio (IRRs) were 2.0 (IQR 1.5–4.1), 1.4 (IQR 0.4–8.8), and 5.4 (IQR 1.7–9.1), respectively.

Deaths among HCWs due to TB have been reported, (Marcus et al., 1997, Pan et al., 2015a, Sepkowitz, 1994, Tudor et al., 2014, von Delft et al., 2016) and although available data do not allow comparisons of mortality risk, but HCWs are at high risk of death if they contract MDR-TB disease (Institute of Medicine, 2001, von Delft et al., 2016). HCWs are up to 6 times more likely to be hospitalized for drug-resistant TB than the population they care for (IRR= 5.46 for MDR and 6.28 for XDR) (O'Donnell et al., 2010). Furthermore, HCWs with drug-resistant TB are diagnosed late and have poor treatment outcomes, even when HIV-uninfected (Jarand et al., 2010, Tudor et al., 2014).

4.2.4 Prevention of tuberculosis in healthcare settings

Given the risk of TB infection among HCWs and patients, and the essential role HCWs play in managing active cases and in preventing further transmission of *M. tuberculosis*, in addition to general infection prevention and control measures, various guidelines have been developed specifically for the prevention of TB in healthcare settings. These include WHO and CDC guidelines (Jensen et al., 2005, World Health Organization, 1999, 2009b). While these guidelines are relatively recent, many of the TB prevention measures in healthcare settings have been proposed long before there was a consensus on the risk of TB for HCWs. Back in 1930, Myers (Myers, 1930) had recommended how best to control TB in hospitals. He suggested five steps that included performing tuberculin testing and chest radiographs on all new employees and doing follow-up testing every 6 to 12 months. Also, excluding TB in all new patients admitted to the hospital, including initiating routine admission chest radiography. Finally, establishing a TB service in all hospitals and practicing aseptic technique as was routine for other infections such as diphtheria and scarlet fever.

The WHO policy on TB infection control recommends four levels of protection: an overarching managerial level, administrative control, environmental control, and personal respiratory protection (World Health Organization, 2009b). Similarly, in the CDC's guidelines, all healthcare settings should have a TB infection control program. The latter should be designed to ensure prompt detection, airborne precautions, and treatment of individuals who have suspected or confirmed TB disease1 and should be based on a three-level hierarchy of controls, including administrative, environmental, and respiratory protection (Jensen et al., 2005).

The facility-level managerial activities recommended by the WHO constitute the framework for setting up and implementing the other controls at facility level. They include identifying and strengthening local coordinating bodies for TB infection control, developing a facility plan for implementation as well as monitoring and evaluating the TB infection control measures. Also, WHO advocates for conducting on-site surveillance of TB disease among HCWs and assess the facility (World Health Organization, 2009b).

Administrative controls are measures aimed at preventing HCWs, other staff, and patients from being exposed to TB and reducing the transmission of infection by ensuring the rapid diagnosis and treatment of patients and staff with TB (Jensen et al., 2005). Administrative controls are the most important level of all protection and control programs as without effective administrative controls, environmental measures and personal respiratory protection are of limited value (Jo, 2017, World Health Organization, 2009b).

Administrative control measures recommended by the WHO and the CDC include prompt identification of people with TB symptoms (triage), isolation of infectious patients, control of the spread of the pathogen (e.g. cough etiquette and respiratory hygiene), and minimization of time spent in health care facilities to significantly reduce the risk of TB transmission by preventing the generation of droplet nuclei (Jensen et al., 2005, World Health Organization, 2009b). Administrative controls also involve baseline and serial screening for LTBI of HCWs at risk for exposure to TB(Jensen et al., 2005, Jo, 2017).

Environmental control measures are the second line of defence for the prevention of nosocomial *M. tuberculosis* transmission to HCWs and are used to reduce the concentration of infectious droplet nuclei to which HCWs or patients may be exposed. A variety of simple to complex environmental controls can be used depending on the design of the healthcare facility, climate of the area, type of patient population served, number of TB patients cared for in the facility, and resources available (World Health Organization, 1999, 2009b). In general, primary environmental controls consist of controlling the source of infection by using local exhaust ventilation (e.g., hoods, tents, or booths) and diluting and removing contaminated air by using general ventilation (e.g. open windows) (Jensen et al., 2005, World Health Organization, 2009b). Secondary environmental controls consist of controlling the airflow to prevent contamination of air in areas adjacent to the source and cleaning the air by using high efficiency particulate air (HEPA) filtration or using ultraviolet germicidal irradiation (UVGI) to kill *M. tuberculosis* (World Health Organization, 2009b).

Administrative and environmental controls minimize the number of areas in which exposure to *M. tuberculosis* might occur and, therefore, minimize the number of persons exposed. These control levels also reduce, but do not eliminate, the risk for exposure in the limited areas in which exposure can still occur. Because persons entering these areas might be exposed to *M. tuberculosis*, the use of respiratory protective equipment in situations that pose a high risk for exposure is the last line of defence for HCWs against nosocomial *MTB* infection (Jensen et al., 2005). Personal respiratory protection refers to "the use of respiratory protective devices by HCWs that fit over the mouth and nose to protect against transmission of *M. tuberculosis* by reducing the risk of inhaling infectious droplet nuclei". Because widespread and constant use of respirators is impractical, it is recommended that they should be used on a limited basis in specified high risk areas in conjunction with other administrative and environmental control measures (World Health Organization, 2009b). To reduce the risk of exposure the CDC recommends the implementation of a respiratory-protection program, training HCWs on respiratory protection, and training patients on respiratory hygiene and cough etiquette procedures (Jensen et al., 2005).

The impact of the various control measures on TB transmission in the healthcare setting is still not well studied specially in low-income settings (Joshi et al., 2006, Menzies et al., 2007). However, in general, evidence suggests that control measures, particularly administrative controls, appear to have an impact on TB transmission (Menzies et al., 2007). Few studies evaluated the impact of infection control strategies on risk of TB infection or disease in low-income settings; therefore, it is difficult to make any inferences regarding the effectiveness of control measures (Joshi et al., 2006). One study found that administrative measures had little impact on the development of TB disease, but after only one year, a relatively short interval to detect changes (Harries et al., 2002). Two other studies reported significant reduction of TB infection within a year following introduction of multiple infection control measures (Roth et al., 2005, Yanai et al., 2003). In studies conducted in high-income countries, indicators of nosocomial transmission rapidly declined following the application of a full hierarchy of recommended infection control measures (Menzies et al., 2007). Due to the simultaneous introduction of the various interventions, identifying a single key measure responsible for decrease transmission is difficult. However, Moro et al. (Moro et al., 2000) reported that in one hospital, implementation of only administrative controls resulted in the complete elimination of MDR-TB transmission. In two other studies, the implementation of administrative controls also resulted in reduced transmission and subsequent implementation of environmental controls led to further decreases (Blumberg et al., 1995, Jarvis, 1995). Other studies also reported decrease in transmission following intervention measures that included environmental controls such as improved ventilation (Behrman and Shofer, 1998, Fridkin et al., 1995).

4.2.5 Knowledge, attitude and practice of healthcare workers in relation to tuberculosis

Advocacy, communication and social mobilization (ACSM) are three distinct sets of activities, all aimed at bringing about behavioral change. In relation to TB, the WHO considers ACSM and important part of TB programs and well-designed and rigorously conducted KAP surveys can produce data that are informative, insightful and broadly useful in the planning of ACSM activities for TB control as well as providing an evidence base for refining and evaluating ACSM work (World Health Organization, 2008a).

In general, a KAP survey is a representative study of a specific population to collect information on what is known (knowledge), believed (attitude) and done (practice) in relation to a particular topic (Wahab et al., 2016). TB KAP surveys can identify knowledge gaps, cultural beliefs, or behavioral patterns and can reveal misconceptions or misunderstandings that may facilitate understanding and action, as well as pose problems or create barriers for TB control efforts. They can identify unknown factors influencing people's behaviour, reasons for their attitudes, and how and why people practice certain health behaviours (World Health Organization, 2008a). Information gained from TB KAP surveys enables decision makers to set TB programs' priorities (e.g. to address the most common or pressing issues or to identify specific subgroups whose needs may differ from other groups), to estimate resources required for various actions, to select the most effective communication channels and messages, to establish baseline levels and measure change that results from TB interventions (World Health Organization, 2008a).

Given the central role HCWs play in diagnosing and managing TB patients and implementing infection prevention and control measures as well as them being an important source of information regarding the disease to patients and the public in general, understanding HCWs KAP with regards to TB and its management is essential. Gaps in knowledge, negative attitudes or wrong practices in relation to TB and its management among HCWs can have detrimental effects not only on the patients they serve but on themselves, the TB program on institutional and national levels as well as on the global population in general. Information collected from TB KAP surveys among HCWs can serve as a basis for identifying difficulties, limitations and capacities for enhancement, and direct resources and efforts towards the appropriate interventions for improvement. Numerous studies reported on knowledge, attitude and/or practice regarding TB, its management or its prevention and control among HCWs from around the world (Bhebhe et al., 2014, Doosti Irani et al., 2015, Engelbrecht et al., 2016, Hashim et al., 2003, Hoffman et al., 2016, Hong et al., 1995, Kiefer et al., 2009, Lai et al., 1996, Malangu and Adebanjo, 2015, Naidoo and Mahommed, 2002, Noe et al., 2017, Singla et al., 1998, Temesgen, 2011, Tenna et al., 2013, van der Werf et al., 2012, Wahab et al., 2016, Woith et al., 2012). These studies report that HCWs have numerous knowledge gaps in relation to TB diagnosis, treatment and infection prevention and control, have some negative attitudes and stigma connected with the disease and engage in poor practices, all of which contribute to their increased risk of infection and negative impacts on patients and the community.

In the context of Hajj, 1000s of HCWs are drafted each year from across the Kingdom of Saudi Arabia (KSA) to deliver healthcare at facilities in Makkah and Madinah for pilgrims arriving from across the world for the pilgrimage. Hajj has been linked to increased risk of TB infection as many pilgrims come from TB endemic countries and both diagnosed and undiagnosed TB among pilgrims were reported (Al-Orainey, 2013, Alzeer et al., 1998, Alzeer, 2009, Wilder-Smith et al., 2005, Yezli et al., 2017b). HCWs serving during Hajj come from different nationalities, educational, institutional and working backgrounds and work in different specialties. Many are deployed to temporary healthcare facilities attending large numbers of patients in a limited period of time. While this workforce receives various trainings in preparation for Hajj work, it is unclear whether this is adequate to improve their collective knowledge, attitude or practice to TB and its management during or after the event.

One study investigated the KAP of HCWs working in Hajj in relation to infect control. Ghabrah et al. (Ghabrah et al., 2007) found that HCWs correctly answered only about half the questions on the knowledge concerning important aspects of standard and transmission based precautions. There was significant deficiency of knowledge regarding the type of isolation precautions required for infections transmitted by droplets and airborne routes, including pulmonary TB, as well as lacks in other important hospital infection control measures. In the self-reported assessment of practice, HCWs reported suboptimal compliance with standard precautions practices, particularly with regard to wearing eye shields and gowns when there is any risk of blood splash and wearing gloves when drawing blood from patients. These results suggest that there is need for more training to improve KAP of HCWs deployed for Hajj in relation to infection control, including TB control. No study specifically investigated KAP of HCWs working in Hajj in relation to TB and its management.

Table 28. Occupational risk of tuberculosis

Categories according to Snider(Snider, 1991)	Categories according to Rodriguez Bayarri and Madrid San Martin(Rodriguez Bayarri and Madrid San Martin, 2004)
Category 1: occupations of workers at high risk of contracting TB **Example** Immigrant workers Laundry workers Food operatives Prison warders Poorly qualified manual workers	**Category 1: Nonoccupational TB-no causal relationship to the workplace** **Example** Immigrants, who congregate in the same jobs and workplaces
Category 2: occupations that increase susceptibility to development of active disease **Example** Work with risk of contact with silica Extraction industries (mines, quarries) Sand-blasting Ceramic industries Iron and steel works Tunneling (civil engineering works)	**Category 2: occupational TB cases with a direct passive causal relationship considered intrinsic to the workplace** **Example** Work done in mines, tunnels, quarries and galleries Cutting or polishing of silica rock Masonry work Dry grinding, sieving and handling of minerals and rocks Production of silicon carbide, glassware, porcelain, earthenware and other ceramic products Production and maintenance of abrasives and other detergent powders Removal of pieces from molds Trimming and desanding in casting Work with grinders (polishing and finishing) that contain free silica Sandblasting and stone polishing. Extraction, handling, and treatment of asbestos minerals or rocks Production of asbestos textiles, card, and paper Preparation of asbestos fibers (combing, spinning, weaving) Pistol application of asbestos (chimneys and car and wagon bases) Work with thermal insulation in shipping and buildings and their demolition Production of brake and clutch pads, fiber cement products, firefighting equipment, and asbestos and rubber seals Disassembly and demolition of facilities that contain asbestos
Category 3: occupations that increase the risk of exposure **Example** Those at risk of contact with TB (people or animals) Geriatric facilities Homeless shelters Healthcare facilities Drug rehabilitation centers Prisons and reformatories Animal research facilities	**Category 3: occupational TB with an active intrinsic causal relationship to the workplace** **Example** Healthcare workers Laboratory workers Veterinary workers Workers with the population of homeless refuges and shelters, prison inmates, and refugees and asylum seekers

TB= tuberculosis

Table 29. Prevalence of latent tuberculosis infection among healthcare workers*

Reference	Country	Year	N	BCG %	TST+ve (%)
He(He et al., 2015)	China	2015	875	36	19.5
McCarthy(McCarthy et al., 2015)	South Africa	2015	199	-	44.7
Adams(Adams et al., 2015)	South Africa	2015	329	92	84
Islam(Islam, 2014)	Bangladesh	2014	449	82	54
de Souza(de Souza et al., 2014)	Brazil	2014	632	86	40
Zhou(Zhou et al., 2014)	China	2014	529	32	43.9
Christopher(Christopher et al., 2014, Rogerio et al., 2013)	India	2014	755	81	45
Rogerio(Rogerio et al., 2013)	Brazil	2013	225	-	24
Zhang(Zhang et al., 2013)	China	2013	96	98	55.2
Wei(Wei et al., 2013)	China	2013	85	94	97.6
Jo(Jo et al., 2013)	South Korea	2013	493	81	36.7
Whitaker(Whitaker et al., 2013)	Georgia	2013	260	90	55.8
Spindola De Miranda(Spindola De Miranda et al., 2012)	Brazil	2012	251	40	60
Zwerling(Zwerling et al., 2012)	Canada	2012	387	36	5.7
Larcher(Larcher et al., 2012)	Italy	2012	549	38	29.1
Freeman(Freeman et al., 2012)	New Zealand	2012	317	67	21.1
Jung(Jung et al., 2012)	South Korea	2012	153	86	15.0
He(He et al., 2012)	Mongolia	2012	917	34	47.9
Teixeira(Teixeira et al., 2011)	Brazil	2011	1032	83	6.9
Severo(Severo et al., 2011)	Brazil	2011	55	98	47.3
Talebi-Taher(Talebi-Taher et al., 2011)	Iran	2011	200	100	52.5
Khoury(Khoury et al., 2011)	USA	2011	611	82	8.2
Torres Costa(Torres Costa et al., 2011)	Portugal	2011	2884	100	72.9
Rafiza(Rafiza et al., 2011)	Malaysia	2011	95	100	58.9
Moon(Moon et al., 2011)	South Korea	2011	156	100	33.3
He(He et al., 2010)	China	2010	2153	36	51.4
Fox(Fox et al., 2009)	Israel	2009	91	37	34.1

Cont..Table 29. Prevalence of latent tuberculosis infection among healthcare workers

Vinton(Vinton et al., 2009)	Australia	2009	341	78	33.4
Girardi(Girardi et al., 2009)	Italy	2009	115	37	53.0
Tripodi(Tripodi et al., 2009)	France	2009	148	100	65.5
Alvarez-Leon(Alvarez-Leon et al., 2009)	Spain	2009	123	35	7.3
Casas(Casas et al., 2009)	Spain	2009	145	16	69.7
Topic(Topic et al., 2009)	Croatia	2009	54	100	63.0
Lee(Lee et al., 2009)	South Korea	2009	196	93	47.4
Lien(Lien et al., 2009)	Vietnam	2009	255	33	63.9
Nienhaus(Nienhaus et al., 2008)	Germany	2008	261	38	24.1
Choi(Choi et al., 2008)	South Korea	2008	80	100	45.0
Mirtskhulava(Mirtskhulava et al., 2008)	Georgia	2008	265	78	66.8
Pai(Pai et al., 2008)	India	2008	719	71	41.4
Rabahi(Rabahi et al., 2007)	Brazil	2007	413	71	51
Soborg(Soborg et al., 2007)	Denmark	2007	139	76	33.8
Hotta(Hotta et al., 2007)	Japan	2007	202	93	59.4
Ozdemir(Ozdemir et al., 2007)	Turkey	2007	76	91	53.9
Kayanja(Kayanja et al., 2005)	Uganda	2005	396	66	57
Pai(Pai et al., 2005)	India	2005	720	71	41
Roth(Roth et al., 2005)	Brazil	2005	4419	67	49
Keskiner(Keskiner et al., 2004)	Turkey	2004	491	93	72
Yanai(Yanai et al., 2003)	Thailand	2003	1202	82	63
Bonifacio(Bonifacio et al., 2002)	Peru	2002	97	-	60
Naidoo(Naidoo and Mahommed, 2002)	South Africa	2002	78	-	33
Alonso-Echanove(Alonso-Echanove et al., 2001)	Peru	2001	270	-	63
Garcia-Garcia(Garcia-Garcia et al., 2001)	Mexico	2001	823	84	34
Plitt(Plitt et al., 2001)	Canada	2001	560	44	46

Cont..Table 29. Prevalence of latent tuberculosis infection among healthcare workers

Stuart(Stuart et al., 2001)	Australia	2001	4070	89	19
Kassim(Kassim et al., 2000)	Ivory cost	2000	512	83	79
Orrett(Orrett, 2000)	Trinidad	2000	182	4	44
Do(Do et al., 1999)	Thailand	1999	911	77	68
Zahnow(Zahnow et al., 1998)	USA	1998	1014	8	24
Menzies(Menzies et al., 1998)	Canada	1998	4651	31	29
Manusov(Manusov et al., 1996)	USA	1996	501	0	4
Bailey(Bailey et al., 1995)	USA	1995	6070	0	11
Molina-Gamboa(Molina-Gamboa et al., 1994)	Mexico	1994	175	80	70
Fraser(Fraser et al., 1994)	USA	1994	351	12	25
Dooley(Dooley et al., 1992)	USA	1992	880	<5	25

*adapted from Joshi et al.(Joshi et al., 2006), Nasreen et al.(Nasreen et al., 2016), Lamberti et al.(Lamberti et al., 2015) and Menzies et al.(Menzies et al., 2007)

LTBI=latent tuberculosis infection, HCW=healthcare worker, BCG=bacille Calmette-Guerin, TST=tuberculin skin test

Table 30. Incidence of latent tuberculosis infection among healthcare workers*

Reference	Country	Year	N	ARTI in HCWs (%)	ARTI attributable to nosocomial transmission (%)
Levy(Levy et al., 2005)	Brazil	2005	46	0.5	0
Maciel(Maciel et al., 2005)	Brazil	2005	76	5.3	4.8
Pai(Pai et al., 2005)	India	2005	147	4.1	2.6
Roth(Roth et al., 2005)	Brazil	2005	1209	8.7	8.2
Yanai(Yanai et al., 2003)	Thailand	2003	331	7.2	5.8
Larsen(Larsen et al., 2002)	USA	2002	5773	0.38	0.28
Miller(Miller et al., 2002)	USA	2002	3248	2.1	1.4
Bonifacio(Bonifacio et al., 2002)	Peru	2002	35	14.3	11.3
Silva(Silva et al., 2002)	Brazil	2002	414	3.9	3.4
Warren(Warren et al., 2001)	USA	2001	731	1	-
Menzies(Menzies et al., 2000)	Canada	2000	1289	1.2	-
Behrman(Behrman and Shofer, 1998)	USA	1998	2514	2	1.8
Blumberg(Blumberg et al., 1998)	USA	1998	2144	1.6	-

Cont... Table 30. Incidence of latent tuberculosis infection among healthcare workers*

Reference	Country	Year	N	ARTI in HCWs (%)	ARTI attributable to nosocomial transmission (%)
Christie(Christie et al., 1998)	USA	1998	28916	0.2	-
LoBue(LoBue and Catanzaro, 1998)	USA	1998	9905	0.6	-
Zahnow(Zahnow et al., 1998)	USA	1998	766	1.8	1.7
Louther(Louther et al., 1997)	USA	1997	898	7.2	7.1
Rullan(Rullan et al., 1996)	Spain	1996	92	10.4	10.1
Bailey(Bailey et al., 1995)	USA	1995	3106	0.9	0.8
Adal(Adal and Hospital, 1994)	USA	1994	11188	0.2	0.1
Ramirez(Ramirez et al., 1992)	USA	1992	6452	0.7	0.6

*adapted from Joshi et al.(Joshi et al., 2006), Nasreen et al.(Nasreen et al., 2016), Baussano et al.(Baussano et al., 2011) and Menzies et al.(Menzies et al., 2007)

LTBI=latent tuberculosis infection, HCW=healthcare worker, ARTI=annual risk of tuberculosis infection

Table 31. Tuberculosis disease among healthcare workers*

Reference	Country	Year	HCWs exposed/TB patients seeking care	Incidence of TB disease in HCWs (per 100,000)	Incidence rate ratio (relative risk) (95% CI)	Risk of TB disease attributable to nosocomial transmission
Naidoo(Naidoo and Jinabhai, 2006)	South Africa	2006	49392/NR	1180	1.6 (1.5 to 1.8)	462
Hosoglu(Hosoglu et al., 2005)	Turkey	2005	734/NR	199.9	5.0 (2.8 to 8.6)	160
Jiamjarasrangsi(Jiamjarasrangsi et al., 2005)	Thailand	2005	3959/NR	188	1.32 (1.0 to 1.7)	46
Dimitrova(Dimitrova et al., 2005)	Russia	2005	64855/2445	81.2	0.7 (0.6–0.9)	-32
Rao(Rao et al., 2004)	India	2004	NR	1260	7.5 (3.9 to 13.2)	1092
Jelip(Jelip et al., 2004)	Malaysia	2004	7312/NR	280.4	2.69 (2.1 to 3.4)	176.4
Gopinath(Gopinath et al., 2004)	India	2004	6016/1174	208	1.2 (1.0 to 1.6)	40
Kanyerere(Kanyerere and Salaniponi, 2003)	Malawi	2003	571/3607	5780	13.8 (9.4 to 19.6)	5361
Eyob(Eyob et al., 2002)	Ethiopia	2002	90/4862	5556	20.0 (6.5 to 47.3)	5279

Cont.. Table 31. Tuberculosis disease among healthcare workers*

Reference	Country	Year	HCWs exposed/TB patients seeking care	Incidence of TB disease in HCWs (per 100,000)	Incidence rate ratio (relative risk) (95% CI)	Risk of TB disease attributable to nosocomial transmission
Harries(Harries et al., 2002)	Malawi	2002	2979/NR	3222	8.3 (6.5 to 10.3)	2833
Cuhadaroglu(Cuhadaroglu et al., 2002)	Turkey	2002	3359/NR	96	3.2 (1.8 to 5.5)	67
Kilinc(Kilinc et al., 2002)	Turkey	2002	6156/NR	69	1.8 (1.2 to 2.7)	28
Alonso-Echanove(Alonso-Echanove et al., 2001)	Peru	2001	2300/NR	391	3.5 (2.4 to 5.1)	280
Krunner(Kruuner et al., 2001)	Estonia	2001	14730/806	91	1.4 (1.0 to 2.0)	25
Skodric(Skodric et al., 2000)	Serbia	2000	267/600	287	4.8 (2.1 to 9.7)	228
Harries(Harries et al., 1999)	Malawi	1999	3042/14532	3550	9.1 (7.3 to 11.3)	3161
Wilkinson(Wilkinson and Gilks, 1998)	South Africa	1998	725/760	506	1.33 (0.8 to 2.0)	127
Balt(Balt et al., 1998)	**South Africa**	**1998**	**NR**	**275**	**0.7 (0.08 to 2.6)**	**-104**
Harries(Harries et al., 1997)	Malawi	1997	310/1112	1935	4.9 (2.5 to 8.8)	1546
Babus(Babus, 1997)	Croatia	1997	170/610	703	9.5 (5.3 to 16.1)	629

*adapted from Joshi et al.(Joshi et al., 2006) and Menzies et al.(Menzies et al., 2007)

TB=tuberculosis, HCW=healthcare worker, CI=confidence interval, NR=not reported

4.3 Aims

The study overall objective is to determine HCWs' knowledge and knowledge gaps regarding TB and its management and attitude and behaviours among HCWs that could facilitate TB transmission or impact TB management.

Specific objectives:

1. To investigate level of knowledge of HCWs regarding TB and its management and their attitudes and behaviours in practice in relation to the disease.
2. To study factors associated with poor knowledge and attitude or bad practice regarding TB and its managements among HCWs.
3. To propose interventions to address knowledge gaps or poor attitudes among HCWs and improve best practices in the management of the disease during the Hajj mass gathering.

4.4 Methods

4.4.1 Study design

A cross sectional study to assess KAP of HCWs working during the Hajj regarding TB and its management.

4.4.2 Study location

The study took place in Makkah, (KSA), the site of the Hajj pilgrimage. It included 13 hospitals situation in the city including Hajj holy sites as shown in Table 2.

4.4.3 Study period

The study was conducted during Hajj season from 2nd to 12th September 2016 corresponding to the 1st to 11th of DulHija 1437 H in the Islamic calendar.

4.4.4 Study population

4.4.4.1 Sample Size

It is estimated that 13,000 HCWs are mobilised during Hajj. The sample size was determined using Epi Info™ using a margin of error of 5%, a CI of 95%, a population size of 13,000, and an expected response rate of 50% to most of the main questions. The minimum sample size estimated for the study was 374. We enrolled a larger sample size of 540 HCWs to account for errors and non-respondents.

4.4.4.2 Eligibility criteria

Inclusion criteria

Inclusion criteria for the study were as follows:

- HCWs (physicians, nurses, pharmacist, laboratory personnel, other) from selected healthcare facilities (Table 2)
- Male and female
- Saudi and non-Saudi
- Willing to participate in the study

Exclusion criteria

Exclusion criteria from the study were as follows:

- Refusal to participate in the study
- Not a HCW

4.4.5 Recruitment and data collection

4.4.5.1 Recruitment Process

The appropriate authorizations were obtained for conducting the study at the selected hospitals prior to starting data collection. Hospital directors were informed of the study, its objectives and the date/times that the research teams will be conducting the study. HCWs were selected randomly without presumption of potential occupational exposure to TB. The research team members distribute and collect the study questioners from HCWs after introducing themselves and explaining the survey's purpose and the objectives of the study.

The questionnaires also had a cover letter that explained the aim and objectives of the study and the research coordinator's contact email and phone number if HCWs had any further queries.

4.4.5.2 Data collection tools

Data was collected using an anonymous self-administered questionnaire developed in both English and Arabic languages (see appendix 4: data collection form for the knowledge, attitude and practice survey of healthcare workers regarding TB). The survey was designed to collect KAP information concerning TB and its management and infection prevention and control measures. The questionnaire was developed by reviewing available questionnaires in the literature (Bhebhe et al., 2014, Kanjee et al., 2011, Malangu and Adebanjo, 2015, Temesgen, 2011) and the WHO guidelines for TB KAP surveys (World Health Organization, 2008a) but was tailored for the Hajj setting and the study objectives. The following was performed to ensure the quality of the data collected:

1. The questionnaire was carefully designed according to the study objectives and reviewed to ensure good understanding of questions and acquiring clear and precise answers. Questions were developed to be as precise and as unambiguous as possible with multiple choices and close-ended questions for accuracy. Study questionnaire was translated to Arabic using a professional certified medical translator. Translated questionnaire was back-translated by someone else other than the first translator to make sure that the translation was as accurate as possible.
2. The questionnaire was piloted prior to the actual date of data collection in places different from the sample settings. The questionnaire was distributed to 20 randomly selected HCWs working in Riyadh. The questionnaire had a comment section related to any unclear questions or sections in the questionnaire so these could be improved in the final version. Final version of the questionnaire was revised carefully. The Cronbach's alpha, (coefficient α), for the knowledge, attitude and practice sections of the final questionnaire were 0.78, 0.72 and 0.86 respectively and were deemed acceptable.

3. The information sheet accompanying the questionnaire was also translated into Arabic using a professional certified medical translator and back-translated for accuracy. The data collected and the quality of the information gathered was reviewed at the end of each day of the study to identify possible issues and improve data quality going forward. The principle investigator provided training for the study team. The aim of such trainings is to ensure that they understood the study objectives, their roles and collecting tool. The training was half day lectures and workshops for 2 days to explain the overall aim of the study, objectives, data collection tools included Clear step by step study instructions were also produced and distributed to the research team in Arabic and English, importance of patients' information and confidentiality as well as the role of each member of the team. The PI conducted a meeting at the end of each day to discuss the challenges and the progress of work

4.4.6 Data entry and cleaning

Data was entered following the gold standard for professional data entry which is double data entry. Data was entered twice in Excel and the two data sets were then compared, differences were examined, errors were verified against the original questionnaires and corrections were made. The data set was then exported to SPSS where frequencies for all variables were generated. The frequency tables generated were then examined to detect unusual values. Final databases were cleaned by the principle investigator to ensure quality before analysis.

4.4.7 Knowledge attitude and practice scores

The KAP questions were scored as follows:

For questions with one possible correct/appropriate answer (including multiple choice questions), a score of 1 was given for choosing the correct/appropriate answer; a correct/appropriate response being that based on current literature and practice. A 0 score was given for choosing the wrong/inappropriate answer, choosing an uncertain response (I don't know) or choosing any combination of correct/appropriate answer, wrong/inappropriate answer or uncertain response.

For multiple-choice questions where more than one correct/appropriate answer was possible, highlighted by the wording “Tick all that apply” in the questionnaire (see appendix 1), the scoring was calculated as follows:

- Respondents were scored 1 point for ticking the correct/appropriate answer, 1 point for not ticking the wrong/inappropriate answer or the uncertain answer (don’t know). Zero score was given for ticking wrong/inappropriate answers, uncertain answers or not ticking the correct/appropriate answer. The total points were summed for each question and a weighed score was generated by dividing the total score of each question by the number of multiple choices in it so that the final score would range between 0 and 1.

- For questions that had a “not applicable” option, the score for each question was as follows: A score of 1 was given for the correct/appropriate answer, and 0 score was given for the wrong/inappropriate answer or a “not applicable” answer.

The overall total knowledge score, attitude score or practice score was computed by totaling the score for each question in the section and a weighed score for each section was generated by diving the overall total score for each section by the number of applicable questions within the section. The number of applicable questions refers to the number of questions in each section that do not include the “not applicable” option. For sections which include the “not applicable” options, the applicable number of questions in each section for each participant was the number of questions answered without ticking the “not applicable” option. This was to ensure that participants who ticked “not applicable” as a reply were not penalised in the final scoring by being counted in the same category as participants who answered the question wrongly/inappropriately. This scoring strategy ensured that overall knowledge score, attitude score or practice score for each participant were weighed correctly and ranged from 0 to 1.

The overall scores were further divided into 5 categories to reflect the level of KAP among HCWS. These were: poor (score 0-0.2), below average (score >0.2-0.4), average (score >0.4-0.6), above average (score >0.6-0.8), good (score >0.8-1).

4.4.8 Statistical analysis

Data was analysed using SPSS 22.0 /and or SAS 9.4 software programme. Descriptive statistics such as frequency, mean, standard deviation (SD), median, minimum and maximum and IQR were computed for quantitative variables and frequencies and percentages were calculated for categorical variables. Cronbach's α, was used to measure reliability and internal consistency for the KAP questions.

To evaluate different variables associated with the knowledge levels, attitude or practice, age was grouped into ordinal categories to facilitate analysis. Demographic variables examined include gender, age groups (<30, 30-39, 40-49, >49), nationality (Saudi, non-Saudi), level of education (diploma, bachelor, master, doctorate/specialty certificate, other), occupation (physician, nurse, other), current job position length (<1 year, 1-5 years, >5-10 years, >10 years), ward stationed in during Hajj and non-Hajj work and contact with TB patients during Hajj or non-Hajj work (Yes, No). The difference of KAP score with respect to individual covariates was evaluated by the non-parametric Mann–Whitney U test or Kruskal-Wallis test as appropriate. Quantile regression was used to investigate the association between variables and the overall KAP scores across the different score levels including the 25th, 50th, and 75th quantiles. Correlation between knowledge attitude and practice was examined using the Spearman correlation coefficient. All of the tests for significance were two-sided and p values < 0.05 were considered statistically significant.

4.4.9 Ethics

The study was approved by the King Fahad Medical City Ethics Committee and the Institutional Review Board (IRB log: 16-329E) (Appendix 5) and by LSTM REC (19-084). All participants gave verbal consent before enrolment and the study was conducted in accordance with the Ethics Committee's guidelines.

4.4.10 Confidentiality

The HCWs KAP survey forms were anonymous and did not include any identifiers or personal information of the participants.

4.5 Results

4.5.1 Demographic characteristics

Data was collected from the 2nd to 12th September 2016 (1st to 11th of Dul-Hijah 1437) from 540 HCWs employed at 13 holy sites hospitals. Characteristics of the study population are summarised in Table 32.

4.5.1.1 Age

Age was recorded for 464 out of the 540 participants (Figure 21). The mean age of recorded respondents was 35.09 (SD= 8.92) years ranging from 22 to 64 years. Age variable was converted into a categorical variable with the following age groups: <30 years, 30-39 years, 40-49 years and >49 years (Table 32). In general, most of the study population was less than 40 years old.

4.5.1.2 Gender

Gender was recorded in 535 individuals. There were 277 (51.8%) females and 258 (48.2%) males in the study sample (Table 32) with a sex ratio of male to female of 1:1.

4.5.1.3 Nationality

Nationality was recorded in 474 HCWs. The highest number of respondents were Saudi nationals 246 (52.1%) (Table 32). Among the non-Saudi nationals, the highest number of HCWs were from the Philippines (63, 27.9%), Egypt (53, 23.5%) and India (31, 13.7%) (Table 33).

4.5.1.4 Level of education

Out of the 529 respondents, most had either a Bachelor degree (237, 44.8%) or a Diploma (191, 36.1%) (Table 32).

4.5.1.5 Occupation

Occupation was recorded in 531 HCWs. Of these, over half (275, 51.8%) were nurses, 154 (29.0%) were physicians and 102 (19.2%) reported their occupation as “other” (Table 32). Among physicians, 18 (11.8%) were general practitioners, 69 (45.1%) were specialists, 44 (28.7%) were residents and 19 (12.4%) were consultants.

Three physicians declared their position to be “other”. Of these one was specialist in diagnostic radiology, one was a psychologist and another was Saudi board certified member. Among the 243 nurses, 8 (3.3%) declared being infection control nurses, while the rest indicated varying areas of work, mainly general (83, 46.6%), ICU (22, 12.4%), surgical (14, 7.8%) and ER (13, 7.3%) nurses. Among the 102 HCWs who reported their occupation as “other”, 48 (47.1%) were laboratory/diagnostic staff, and 35 (34.3%) were pharmacists. Another 19 HCWs reported work in other specialties, one being an epidemiologist and 3 working in respiratory therapy. The rest did not specify their work area.

4.5.1.6 Non-Hajj employment

Experience in current (non-Hajj) employment position

HCWs were asked how long they have been working in their current non-Hajj position. The majority had from 1-5 years' experience (177, 33.9%) or >5-10 years' experience (169, 32.4%). Few (30, 5.7%) had <1 year work experience (Table 32).

Ward stationed in during non-Hajj employment

HCWs were questioned on the wards they are stationed in at their healthcare facilities during non-Hajj work. Of the respondents, 76 (14.4%) worked in ICUs, 110 (20.9%) worked in ERs, 91 (17.3%) worked in medical words, 50 (9.5%) worked in isolation wards, 81 (15.4%) worked in surgical wards, 24 (4.57%) worked in pediatric wards, 24 (4.57%) worked in maternity (O&G) wards and 203 HCWs declared being positioned in other wards not listed in the questionnaire. Of the latter, the majority were stationed in laboratory and blood bank departments (42, 20.6%), outpatients departments (39, 19.1%), radiology departments (25, 12.2%) or in pharmacies (26, 12.7%).

4.5.1.7 Hajj employment

Ward stationed in during Hajj employment

HCWs were questioned on the wards they are stationed in at their healthcare facilities during Hajj work. Of the respondents, 72 (13.9%) worked in ICUs, 149 (28.8%) worked in ERs, 112 (21.6%) worked in medical words, 48 (9.3%) worked in surgical wards, 6 (1.1%) worked in pediatric wards, 5 (0.1%) worked in maternity (O&G) wards and 188 HCWs declared being positioned in other wards not listed in the questionnaire. Of the latter, the majority were stationed in laboratory and blood bank departments (49, 26.8%), outpatients departments (67, 36.6%), radiology departments (25, 13.6%) or in pharmacies (27, 14.8%).

4.5.1.8 Contact with tuberculosis patients during employment

HCWs were asked if they do/did come into contact with TB patients during their Hajj or non-Hajj duties. The results are shown in Table 32.

4.5.1.9 Contact with tuberculosis patients during non-Hajj employment

Of the 510 HCWs who reported on their contact with TB patients during their non-Hajj duties, 261 (51.2%) declared that they do come into contact with TB patients.

4.5.1.10 Contact with tuberculosis patients during Hajj employment

Of the 469 HCWs who reported on their contact with TB patients during their Hajj duties, 85 (18.1%) declared that they did come into contact with TB patients during Hajj work.

Figure 21. Histogram for age of healthcare workers in years

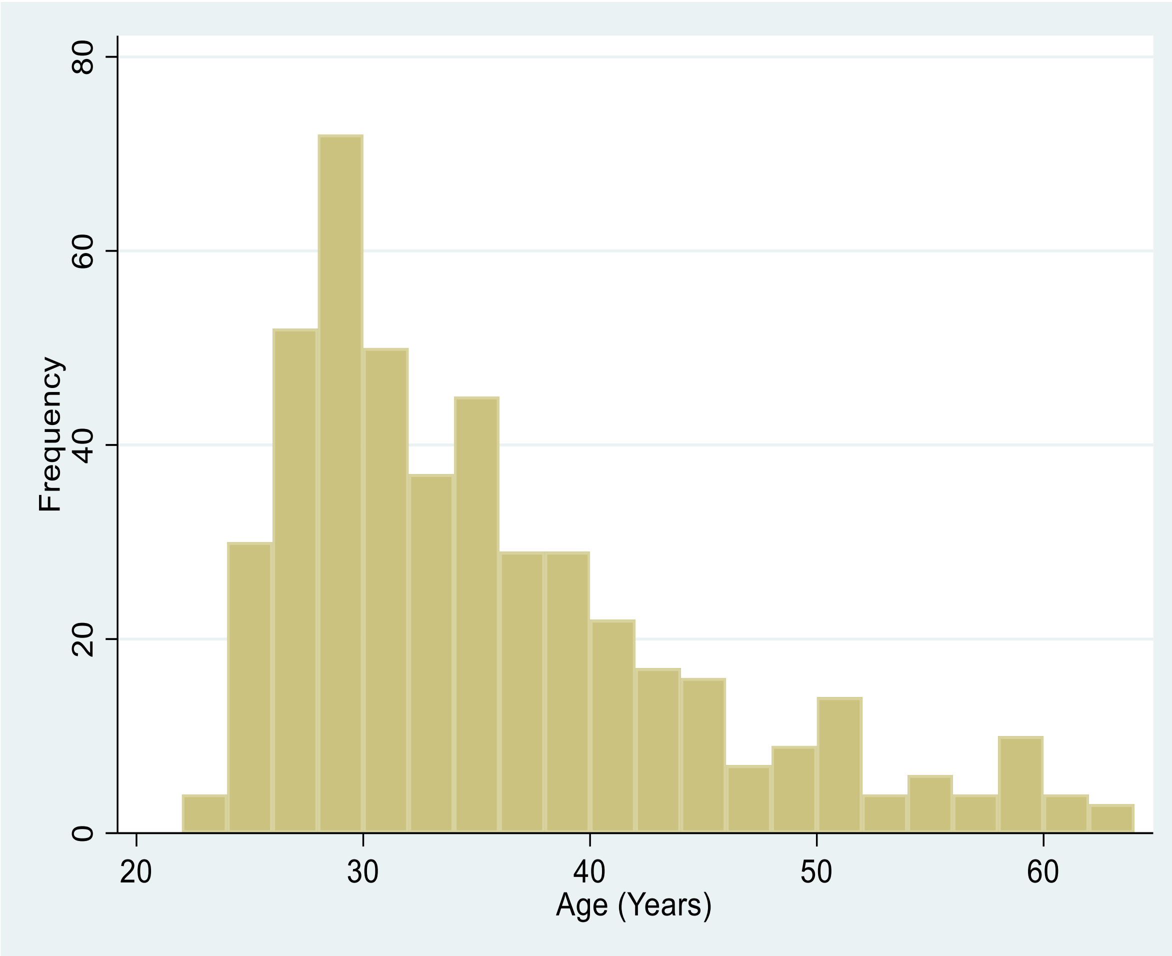


Table 32. Characteristics of the study population

Overall Summary	Category	Freq	%
Age			
	<30	158	34.10
	30-39	190	40.90
	40-49	71	15.30
	>49	45	9.70
Gender			
	Female	277	51.78
	Male	258	48.22
Nationality			
	Saudi	246	52.10
	Non-Saudi	226	47.90
Education Level			
	Other	8	1.51
	Diploma	191	36.11
	Bachelor	237	44.80
	Master	53	10.02
	Doctorate/Specialty certificate	40	7.56
Occupation			
	Other	102	19.21
	Physician	154	29.00
	Nurse	275	51.79
Current position length			
	<1 year	30	5.76
	1 - 5 years	177	33.97
	>5 - 10 years	169	32.44
	>10 years	145	27.83

Cont. Table 32. Characteristics of the study population

Overall Summary	Category	Freq	%
Non-Hajj TB patients contact			
	No	249	48.82
	Yes	261	51.18
Ward in Hajj work			
	ICU	72	13.93
	ER	149	28.82
	Medical ward	112	21.66
	Surgical ward	48	9.28
	Paediatrics ward	6	1.16
	Maternity (O&G) ward	5	0.97
	Other	188	36.86
Hajj TB patients contact			
	No	384	81.88
	Yes	85	18.12

ICU=intensive care unit, ER= emergency room, O&G=obstetrics and gynaecology, TB= tuberculosis, Freq=frequency

Table 33. Nationality of the non-Saudi Healthcare workers in the study

Nationality	Frequency	Percentage (%)
Bangladeshi	4	1.8
Chinese	1	0.4
Egyptian	53	23.5
Filipino	63	27.9
Indian	31	13.7
Indonesian	2	0.9
Jordanian	11	4.9
Lebanese	1	0.4
Pakistani	22	9.7
Palestinian	3	1.3
Sudanese	26	11.5
Syrian	5	2.2
Thai	1	0.4
Tunisian	1	0.4
Turkish	1	0.4
Yemeni	1	0.4
Total	226	100.0

4.5.2 Tuberculosis knowledge among healthcare workers

4.5.2.1 Personal development in relation to knowledge about tuberculosis among healthcare workers

To assess if HCWs were regularly attending information sessions regarding TB and its management to help maintain their knowledge and best practice as well as being aware of the recent knowledge in the area, HCWs were asked if they have attended a lecture / seminar / workshop on TB in the previous 12 months. Results showed that of the 523 respondents, only 129 (24.7%) attended a lecture, seminar or a workshop on TB in the previous year. Of these, 45.7% were nurses and 26.3% were physicians.

4.5.2.2 Knowledge questions regarding tuberculosis

HCWs were asked 23 questions to assess their knowledge regarding TB and its management. These questions were related to:

1. What type of infection is pulmonary TB (PTB) infection
2. Main symptoms of PTB
3. Diagnostic tests for PTB
4. Mode of transmission of PTB
5. Screening tests for LTBI
6. Percentage of active PTB positive for TB on smear microscopy
7. Most useful sputum collection method for PTB diagnosis
8. 1st-line anti-TB drugs
9. 2nd-line anti-TB drugs
10. Definition of MDR-TB
11. Definition of XDR-TB
12. Length of standard treatment of drug-sensitive TB
13. Whether or not HIV patients are more vulnerable to contracting TB
14. Whether or not PTB is curable
15. Whether or not MDR-TB is curable
16. Whether or not BCG vaccination was protective against TB

17. Whether or not PTB is transmitted via the airborne route
18. Latent TB spread
19. Whether or not patients with LTBI have positive reaction on TST/IGRA tests
20. Whether or not patient with TB become non-infectious soon after initiating appropriate treatment
21. Whether or not only patients with active TB can spread the disease
22. Appropriate Personal Protective Equipment (PPE) to use with active PTB patients
23. Importance of using PPE to protect HCWs from TB infection

The results are presented in Table 34.

What type of infection is pulmonary tuberculosis infection?

Over 75% of HCWs correctly identified TB as a bacterial infection (Table 34). However, 101 (20.8%) thought TB was caused by a virus. Among the 121 HCWs who did not identify TB as a bacterial infection, most were nurses (67%) and reported a diploma as their highest level of education (72.2%). Physicians represented only 4.1% of HCWs who did not identify TB as a bacterial infection. Of the HCWs who declared that they deal with TB patients during their non-Hajj work (n= 239), 21.3% provided the wrong answer to the question.

Main symptoms of pulmonary tuberculosis

HCWs were presented with a list of symptoms and were asked to tick all which they thought were main symptoms of PTB. Nearly all HCWs (97.9%) answered the question regarding TB symptoms. The percentage of HCWs who identified symptoms as those of PTB were: 79.2% for cough ≥3 weeks, 63.1% for fever/chill, 9.4% for dizziness, 46.7% for tiredness/fatigue, 75.6% for cough with blood, 71.3% for weight loss, 16.3% for headache, 1.9% for pain when urinating, 9.2% for diarrhoea, 40.2% for chest pain, 56.7% for loss of appetite, 1.3% for memory loss, 52.7% for night sweats and 2.1% for blurry vision. Overall, only 3.6% (19/521) of HCWs correctly identified all the main symptoms of PTB in the list of options, 66.6% of whom were physicians. When analysis was restricted to physicians only, in general the percentage of individuals who correctly identified the main symptoms of TB increased.

The percentage of physicians who identified symptoms as those of PTB were: 88.7% for cough ≥3 weeks, 75.5% for fever/chill, 13.9% for dizziness, 66.9% for tiredness/fatigue, 80.8% for cough with blood,88.7% for weight loss, 19.8% for headache, 1.9% for pain when urinating, 7.9% for diarrhoea, 39.0% for chest pain, 76.8% for loss of appetite, 2.1% for memory loss, 80.1% for night sweats and 5.9% for blurry vision.

Diagnostic tests for pulmonary tuberculosis

HCWs were presented with a number of tests and were asked to identify which test(s) is/are used to diagnose PTB in practice. Most, (97.4%) answered the question, while 14 HCWs declared they did not know the answer (Table 34). Among those who answered the questions, the proportion of HCWs who identified the various tests as diagnostic tests for PTB were as follows: 65.7% for TST, 69.4% for sputum culture, 2.9% for urine examination, 11.9% for the GeneXpert MTB/RIF test, 57.6% for sputum acid-fast bacilli (AFB) smear test, 13.3% for IGRA, 8.3% for liver function test, 13.1% for complete blood count (CBC), 11.8% for blood culture and 71.3% for chest X-ray. Overall, only 1.6% (8/520) HCWs correctly identified all the diagnostic tests for PTB from the list of options.

Mode of transmission of pulmonary tuberculosis

HCWs were asked about the mode of transmission of PTB and 529 (97.9%) answered the question. The proportion of HCWs who identified the various transmission modes as those for PTB were as follows: 9.6% for blood transmission, 93.0% for coughing, 27.0% for sharing food or drink, 41.8% for contaminated surfaces, 65.0% for sneezing, 36.9% for kissing and 16.8% for hand shaking. Overall, only 7% (37/529) of HCWs correctly identified all the modes of transmission of PTB in the listed options.

Screening tests for latent tuberculosis infection

HCWs were presented with a list of tests and were asked to identify which test(s) is/are used to screen for LTBI in practice. Most, (92.8%) answered the question, while 38 HCWs declared they did not know the answer (Table 34).

Among those who answered, the proportion of HCWs who identified the various tests as screening tests for LTBI was as follows: 60.0% for TST, 44.4% for sputum culture, 2.3% for urine examination, 7.2% for the GeneXpert MTB/RIF test, 35.3% for sputum AFB smear test, 12.7% for IGRA, 5.1% for liver functiontest, 7.8% for CBC, 6.2% for blood culture and 53.0% for chest X-ray. Overall only one nurse correctly identified all the screening tests for LTBI in the list of options.

Percentage of active pulmonary tuberculosis positive for tuberculosis on smear microscopy

HCWs were questioned regarding the usual percentage of active PTB positive for TB on smear microscopy. All HCWs answered the question but over half (292, 54.1%) reported that they did not know the answer (Table 34). The majority of the rest thought that the percentage of active PTB that would be positive for TB on smear microscopy was 80% (112, 20.7%) or 50% (88, 16.3%). Out of the 48 HCWs who reported their occupation as laboratory/diagnostic staff, only 18.7% correctly chose 50% as their answer.

Most useful sputum collection method for pulmonary tuberculosis diagnosis

HCWs were asked about the best timing/collection methods of sputum for TB diagnosis. Of the 524 HCWs who answered, 88 (16.8%) declared that they did not know the answer (Table 34). The proportion of HCWs who identified the various sputum timing/collection methods to be the most useful for TB diagnosis was as follows: 87.4% for 3 samples (spot, morning, spot), 6.4% for 3 samples (2 spot, 1 spot), 4.1% for a spot sample, and 2.3% for 2 spot samples.

First line anti- tuberculosis drugs

HCWs were asked to identify the 1st-line anti-TB drugs from a list of options. Of those who answered (526 HCWs), 145 (27.6%) declared that they did not know the answer (Table 34). The proportion of HCWs who identified the various antibiotics as the 1st-line anti-TB drugs was as follows: 78.5% for INH, 83.5% for RIF, 9.4% for CIP, 54.9% for PZA, 2.1% for LEV, 3.7% for KAN, 3.1% for AMK, 58.0% for EMB and 1.3% for CAP. Overall, only 6% (23/381) correctly identified all the 1st-line anti-TB drugs (INH, RIF, PZA and EMB) in the list of options.

When analysis was restricted to physicians only, in general the percentage of individuals who correctly identified the 1st-line anti-TB drugs increased. The proportion of physicians who identified the various antibiotics as the 1st-line anti-TB drugs was as follows: 88.9% for INH, 89.7% for RIF, 3.6% for CIP, 62.5% for PZA, 0.7% for LEV, 2.2% for KAN, 0.74% for AMK, 66.9% for EMB and 0.0% for CAP.

Second-line anti- tuberculosis drugs

HCWs were asked to identify the 2nd-line anti-TB drugs from a list of options. Of those who answered (505 HCWs), 197 (39.0%) declared that they did not know the answer (Table 34). The proportion of HCWs who identified the various antibiotics as the 2nd-line anti-TB drugs was as follows: 31.2% for INH, 30.2% for RIF, 32.5% for CIP, 27.6% for PZA, 16.6% for LEV, 26.6% for KAN, 27.3% for AMK, 28.2% for EMB and 15.9% for CAP. Overall, 4.5% (14/308) of HCWs correctly identified all the 2nd-line TB drugs (CIP, LEV, KAN, AMK and CAP) in the list of options. When analysis was restricted to physicians only, the percentage of individuals who correctly identified the 2nd-line anti-TB drugs increased. The proportion of physicians who identified the various antibiotics as the 2nd-line anti-TB drugs was as follows: 21.2% for INH, 21.2% for RIF, 46.0% for CIP, 20.3% for PZA, 26.5% for LEV, 37.1% for KAN, 40.7% for AMK,, 17.7% for EMB and 27.4% for CAP.

Definition of multidrug-resistant tuberculosis

HCWs were questioned regarding the definition of MDR-TB. Of those who answered (501 HCWs), 206 (41.1%) declared that they did not know the answer (Table 34). A quarter (25.0%) of HCWs correctly identified that MDR-TB is cause by bacteria resistant to at least INH and RIF, The proportion of HCWs who noted various other definitions as the definition of MDR-TB was as follows: 3.8% for resistance to INH, 2.4% for resistance to RIF, 1.6% for resistance to EMB, 2.6% for resistance to at least CIP and KAN and 2.4% for a combination of the various options. A further 106 HCWs (21.2%) thought that the definition of MDR-TB included all the above possibilities. Of the 125 HCWs who correctly identified the definition of MDR-TB, 52.0% were physicians and 33.6% were nurses. Of the HCWs who declared that they deal with TB patients during their non-Hajj work (n= 240), 25.8% knew the definition of MDR-TB.

Definition of extensively drug-resistant tuberculosis

HCWs were questioned regarding the definition of XDR-TB. Of those who answered (479 HCWs), 259 (54.1%) declared that they did not know the answer (Table 34). The proportion of HCWs who noted the various definitions as the definition of XDR-TB was as follows: 12.7% for MDR-TB resistant to any fluoroquinolone and at least one of three injectable 2nd-line drugs (correct answer), 21.1% for TB resistant to all 1st-line anti-TB drug and 11.3% for TB resistant to any fluoroquinolone and at least one of three injectable 2nd-line drugs. Four (0.8%) of HCWs answered a combination of the various options above. Of the 61 HCWs who chose the correct definition of XDR-TB, 46.5% were physicians and 47.4% were nurses. Of the HCWs who declared that they deal with TB patients during their non-Hajj work (n= 234), 14.1% ticked the correct definition of XDR-TB.

Length of standard treatment for new patient with drug-sensitive tuberculosis

HCWs were questioned regarding the standard treatment duration for a new patient with drug-sensitive TB. Of those who answered (513 HCWs), 108 (21.1%) declared that they did not know the answer (Table 34). The proportion of HCWs who picked various treatment durations was as follows: 18.5% for 1-3 months, 23.8% for 4-6 months, 31.0% for 6-9 months (correct answer) and 5.1% for greater than 12 months. Three HCWs (0.5%) answered a combination of the various options above. Out of the 154 physicians, 44.1% correctly answered the question.

Are human immunodeficiency virus patients more vulnerable to contracting tuberculosis?

HCWs were questioned about whether HIV patients were more vulnerable to contracting TB. Of those who answered (519 HCWs), 62 (11.9%) declared that they did not know the answer (Table 34). Most HCWs (422, 81.3%) thought that HIV patients were more vulnerable to contracting TB.

Is pulmonary tuberculosis a curable disease

HCWs were questioned if they thought PTB was a curable disease. Of those who answered (517 HCWs), 39 (7.5%) declared that they did not know the answer (Table 34). Most HCWs (456, 88.2%) thought that PTB was a curable disease, while 22 (4.3%) did not think it was curable. Of the 61 HCWs who did not know the answer to the question or thought TB was not curable, 18.3% were physicians and 53.3% were nurses.

Is multidrug-resistant tuberculosis a curable disease

HCWs were questioned if they thought MDR-TB was a curable disease. Of those who answered (504 HCWs), 161 (31.9%) declared that they did not know the answer (Table 34). About half of the HCWs (256, 50.8%) thought that MDR-TB was a curable disease, while 87 HCWs (17.3%) did not think it was curable. Of the 248 HCWs who did not know the answer to the question or thought MDR-TB was not curable, 21.9% were physicians and 51.6% were nurses.

Bacilli Calmette-Guerin vaccination and protection against developing active tuberculosis

HCWs were questioned about whether people who had received BCG vaccination were protected against developing active TB. Of those who answered (514 HCWs), 140 (27.2%) declared that they did not know the answer (Table 34). Similar proportions of HCWs (36.8% and 36.0% respectively) thought BCG was protective or not protective.

Pulmonary tuberculosis is transmitted via the airborne route

HCWs were questioned about whether the airborne was a mode of transmission of PTB. Of those who answered (507 HCWs), 39 (7.7%) declared that they did not know the answer (Table 34). Most HCWs (424, 83.6%) correctly thought TB was transmitted via the airborne route. Of the HCWs who declared that they deal with TB patients during their non-Hajj work (n= 246), 86.6% provided the correct answer.

Latent tuberculosis and spread of tuberculosis

HCWs were asked if a patient with latent TB can transmit the disease. Of those who answered (515 HCWs), 62 (12.0%) declared that they did not know the answer (Table 34). Over half of the HCWs (284, 55.1%) thought that a patient with latent TB can spread the disease.

A patient with latent tuberculosis has a positive reaction to tuberculin skin test or interferon-gamma release assay

HCWs were asked if a patient with latent TB would have a positive TST or IGRA tests results. Of those who answered (505 HCWs), 160 (31.7%) declared that they did not know the answer (Table 34). Over half of the HCWs (290, 57.4%) thought that a patient with latent TB would have a positive result in a TST or an IGRA test.

Tuberculosis patients become non-infectious soon after initiating the appropriate treatment

HCWs were asked whether TB patients become non-infectious soon after initiating the appropriate treatment. Of those who answered (512 HCWs), 76 (14.8%) declared that they did not know the answer (Table 34). About 40% of HCWs thought that patients with TB would become non-infectious soon after initiating appropriate treatment.

Only patient with active tuberculosis can spread the disease

HCWs were asked if only patients with active TB can spread the disease. Of those who answered (511 HCWs), 63 (12.3%) declared that they did not know the answer (Table 34). About 60% of HCWs thought that only patients with active TB can spread the disease.

Appropriated personal protective equipment to be use when dealing with a patient with active pulmonary tuberculosis

HCWs were asked to identify the most appropriated PPE to be used when dealing with patients with active PTB from a list of options or if PPE was needed at all. Of those who answered (514 HCWs), 25 (4.9%) declared that they did not know the answer (Table 34). Most HCWs (393, 76.5%) believed that N95 respirators should be used when dealing with PTB patients. About 18% thought that surgical masks should be used, while 4 (0.8%) HCWs thought no PPE was necessary. Of the HCWs who declared that they deal with TB patients during their non-Hajj work (n= 250), 82% provided the correct answer to the question.

Importance of using personal protective equipment to protect healthcare workers from tuberculosis

HCWs were questioned about the importance of using PPE when dealing with patients with TB. Of those who answered (522 HCWs), 29 (5.6%) declared that they did not know the answer (Table 34). Most HCWs (469, 89.8%) believed that using PPE to protect HCWs when dealing with TB patients was important, while 24 (4.6 %) thought it was not important. Of those who did not know the answer or thought PPE was not important when dealing with TB patients, 41.5% were doctors and 35.8% were nurses. Of the HCWs who declared that they deal with TB patients during their non-Hajj work (n= 254), 91.3% declared that using PPE was important when dealing with TB patients.

Table 34. Summary statistics of knowledge questions regarding tuberculosis among healthcare workers

Knowledge question	Category	Freq	%
1. TB falls under			
	Viral infection	101	20.82
	Bacterial infection	364	75.05
	Don't know	19	3.92
	Both	1	0.21
2. PTB main symptoms			
	Don't know	11	2.07
	Answered	520	97.93
	Cough ≥3 weeks	412	79.23
	Fever/chills	328	63.08
	Dizziness	49	9.42
	Tiredness/ fatigue	243	46.73
	Cough with blood	393	75.58
	Weight loss	371	71.35
	Headache	84	16.15
	Pain with urination	10	1.92
	Diarrhoea	48	9.23
	Chest pain	209	40.19
	Loss of appetite	295	56.73
	Memory loss	7	1.35
	Night sweats	274	52.69
	Blurry vision	11	2.12

Cont.. Table 34. Summary statistics of knowledge questions regarding tuberculosis among healthcare workers

Knowledge question	Category	Freq	%
3. PTB diagnostic tests			
	Don't know	14	2.63
	Answered	519	97.37
	TST	341	65.70
	Sputum culture	360	69.36
	Urine examination	15	2.89
	GeneXpert MTB/RIF	62	11.95
	Sputum AFB smear	299	57.61
	IGRA	69	13.29
	Liver function	43	8.29
	CBC	68	13.10
	Blood culture	61	11.75
	Chest X-ray	370	71.29
4. PTB transmission			
	Answered	529	97.9
	Blood transmission	51	9.64
	Coughing	492	93.01
	Sharing food or drink	143	27.03
	Contaminated surfaces	221	41.78
	Sneezing	344	65.03
	Kissing	195	36.86
	Shaking hand	89	16.82

Cont.. Table 34. Summary statistics of knowledge questions regarding tuberculosis among healthcare workers

Knowledge question	Category	Freq	%
5. Latent TB screening tests			
	Don't know	38	7.24
	Answered	487	92.76
	TST	292	59.96
	Sputum culture	216	44.35
	Urine examination	11	2.26
	GeneXpert MTB/RIF	35	7.19
	Sputum AFB smear	172	35.32
	IGRA	62	12.73
	Liver function	25	5.13
	CBC	38	7.80
	Blood culture	30	6.16
	Chest X-ray	258	52.98
6. Percentage of active PTB positive for TB on smear microscopy			
	10%	24	4.40
	20%	24	4.40
	50%	88	16.3
	80%	112	20.7
	Don’t know	292	54.1
7. Most useful sputum collection method for PTB diagnosis			
	Don't know	88	16.83
	Answered	436	83.17
	3 samples (spot-morning-spot)	380	87.36
	2 spot, 1 spot samples	28	6.44
	1 spot sample	18	4.14
	2 spot samples	10	2.30

Cont.. Table 34. Summary statistics of knowledge questions regarding tuberculosis among healthcare workers

Knowledge question	Category	Freq	%
8. 1st-line anti-TB drugs			
	Don't know	145	27.57
	Answered	381	72.43
	INH	299	78.48
	RIF	318	83.46
	CIP	36	9.45
	LEV	8	2.10
	CAP	5	1.31
	KAN	14	3.67
	EMB	221	58.01
	PZA	209	54.86
	AMK	12	3.15
9. 2nd-line anti-TB drugs			
	Don't know	197	39.01
	Answered	308	60.99
	INH	96	31.17
	RIF	93	30.19
	CIP	100	32.47
	LEV	51	16.56
	CAP	49	15.91
	KAN	82	26.62
	EMB	87	28.25
	PZA	85	27.60
	AMK	84	27.27

Cont. Table 34. Summary statistics of knowledge questions regarding tuberculosis among healthcare workers

Knowledge question	Category	Freq	%
10. MDR-TB bacteria is resistant to			
	INH	19	3.79
	RIF	12	2.40
	At least INH & RIF	125	24.95
	EMB	8	1.60
	At least CIP & KAN	13	2.59
	All of the above	106	21.16
	Don't know	206	41.12
	Any combinations of the above	12	2.40
11. XDR-TB is			
	Don't know	259	54.07
	MDR-TB resistant to any fluoroquinolone and at least one of three injectable 2nd-line drugs	61	12.73
	TB resistant to any fluoroquinolone and at least one of three injectable 2nd-line drugs	54	11.27
	TB resistant to all 1st-line anti-TB drugs	101	21.09
	Any combinations of the above	4	0.84
12. Length of standard treatment of drug-sensitive TB			
	Don't know	108	21.05
	1-3 Months	95	18.52
	4-6 Months	122	23.78
	6-9 Months	159	30.99
	>12 Months	26	5.07
	Any combinations of the above	3	0.58

Cont.. Table 34. Summary statistics of knowledge questions regarding tuberculosis among healthcare workers

Knowledge question	Category	Freq	%
13. HIV patients are more vulnerable to contracting TB			
	Don't know	62	11.95
	True	422	81.31
	False	35	6.74
14. PTB is curable			
	Don't know	39	7.54
	True	456	88.2
	False	22	4.26
15. MDR-TB is curable			
	Don't know	161	31.94
	True	256	50.79
	False	87	17.26
16. BCG vaccination is protective against TB			
	Don't know	140	27.24
	True	189	36.77
	False	185	35.99
17. PTB is transmitted via the airborne route			
	Don't know	39	7.69
	True	424	83.63
	False	44	8.68
18. Patients with latent TB can spread the disease			
	Don't know	62	12.04
	True	284	55.15
	False	169	32.82

Cont.. Table 34. Summary statistics of knowledge questions regarding tuberculosis among healthcare workers

Knowledge question	Category	Freq	%
19. Patients with latent TB have positive reaction on TST/IGRA tests			
	Don't know	160	31.68
	True	290	57.43
	False	55	10.89
20. Patient with TB become non-infectious soon after initiating appropriate treatment			
	Don't know	76	14.84
	True	208	40.63
	False	228	44.53
21. Only patients with active TB can spread the disease			
	Don't know	63	12.33
	True	306	59.88
	False	142	27.79
22. Appropriate PPE to use with active PTB patients			
	Don't know	25	4.86
	Surgical mask	92	17.9
	N95 respirator	393	76.46
	No PPE is needed	4	0.78
23. Using PPE to protect HCWs from TB is important			
	Don’t know	29	5.56
	Yes	469	89.85
	No	24	4.60

TB=tuberculosis, PTB=pulmonary tuberculosis, HIV=human immunodeficiency virus, PPE=personal protective equipment, HCW=healthcare worker, MDR= multidrug-resistant, XDR=extensively drug-resistant, TST=tuberculin skin tests (TST), AFB=acid-fast bacilli, IGRA= interferon gamma release assay, CBC= complete blood count, INH=Isoniazid, RIF; Rifampicin, CIP=Ciprofloxacin, PZA=Pyrazinamide, LEV=Flevofloxacin, KAN=Kanamycin, AMK=Amikacin, EMB=Ethambutol , CAP=Capreomycin, BCG=Bacillus Calmette-Guéri

4.5.2.3 Knowledge section scores

The mean scores for each knowledge question (min 0, max 1) are presented in Table 35.

Table 35. Mean knowledge scores for healthcare workers regarding tuberculosis and its management

Knowledge question	N	Min	Max	Mean	SD
TB falls under	485	0	1	0.75	0.43
PTB main symptoms	520	0.40	1	0.76	0.14
PTB diagnostic tests	519	0.27	1	0.68	0.13
PTB transmission	540	0.29	1	0.71	0.15
Latent TB screening tests	487	0.27	1	0.74	0.11
Percentage of active PTB positive for TB on smear microscopy	540	0	1	0.16	0.37
Most useful sputum collection method for PTB diagnosis	435	0	1	0.87	0.33
1st-line anti-TB drug	381	0.40	1	0.85	0.10
2nd-line anti-TB drug	308	0.10	1	0.50	0.24
MDR-TB bacteria is resistant to	501	0	1	0.25	0.43
XDR-TB is	479	0	1	0.13	0.33
Length of standard treatment of drug-sensitive TB	513	0	1	0.31	0.46
HIV patients are more vulnerable to contracting TB	519	0	1	0.81	0.39
PTB is curable	517	0	1	0.88	0.32
MDR-TB is curable	504	0	1	0.51	0.5
BCG vaccination is protective against TB	514	0	1	0.36	0.48
PTB is transmitted via the airborne route	507	0	1	0.84	0.37
Patients with latent TB can spread the disease	515	0	1	0.33	0.47
Patients with latent TB have positive reaction on TST/IGRA tests	505	0	1	0.57	0.49
Patient with TB become non-infectious soon after initiating appropriate treatment	512	0	1	0.41	0.49
Only patients with active TB can spread the disease	511	0	1	0.60	0.49
Appropriate PPE to use with active PTB patients	514	0	1	0.82	0.38
Using PPE to protect HCWs from TB is important	522	0	1	0.90	0.30

TB; tuberculosis, PTB; pulmonary tuberculosis, HIV; human immunodeficiency virus, PPE; personal protective equipment, HCW; healthcare worker, MDR; multidrug-resistant, XDR; extensively drug-resistant, TST: tuberculin skin tests (TST), AFB; acid-fast bacilli, IGRA; interferon gamma release assay, CBC; complete blood count, BCG; Bacillus Calmette-Guérin, Min; minimum, Max, maximum, SD; standard deviation, N; number of observations

4.6 Attitude of healthcare workers towards tuberculosis

Information on HCWs' attitude toward TB was collected by asking the following 11 questions/statements:

1. Would you be willing to work in a TB clinic/ward?
2. Would you resign from work if you are posted to a TB clinic/ward?
3. Would you be willing to be screened for TB if you had suggestive symptoms?
4. Do you think all TB patients should be isolated for treatment?
5. It is ok to allow a TB patient to leave the hospital soon after initiating appropriate treatment
6. Would you be willing to attend seminars on TB?
7. Would you recommend the suspension of treatment if a TB patient is feeling better?
8. Would you start TB treatment for a TB patient before diagnosis is confirmed if a suspected TB patient is very ill?
9. Would you use a face mask when dealing with a PTB patient even when it is uncomfortable?
10. Would you trust the result the laboratory provides you on sputum cultures?
11. I would not accept to examine/treat TB patients

The answers to the questions were coded in the database (section) to reflect whether the participants have a positive or a negative attitude and used to calculate the overall attitude scores. Participants were also presented with 4 further questions/statements relating to their perception about the risk of TB infection related to their work and their willingness to teach others in relation to TB. These were the following:

1. I have a very low risk of acquiring TB from my patients
2. I worry about acquiring active TB disease while at work
3. Would you be willing to teach patients and co-workers about TB prevention?
4. Would you be willing to teach patient how to collect sputum sample?

Response to these 4 questions were not included in the calculation of the overall attitude scores.

4.6.1 Individual questions about attitude towards tuberculosis

Results of response to attitude questions are summarised in Table 36.

Would you be willing to work in a tuberculosis clinic/ward?

Of those who answered the question (521 HCWs), 309 (59.3%) declared that they would not be willing to work in a TB clinic or ward. The percentage of doctors who declared they were not willing to work in a TB clinic was slightly higher than that of nurses (60.1% vs 58.2% respectively).

Would you resign from work if you are posted to a tuberculosis clinic/ward?

Of those who answered the question (515 HCWs), 433 (84.1%) declared that they would not resign from their work if they were to be posted to a TB clinic or ward, yet 82 HCWs declared that they would resign. The proportion of nurses who would resign if posted to a TB clinic was slightly higher than that for physicians (16.1% vs 14.4% respectively).

Would you be willing to be screened for tuberculosis if you had suggestive symptoms?

Of those who answered the question (512 HCWs), most, 483 (94.3%), declared that they would be willing to be screened for TB if they had suggestive symptoms. The proportion of HCWs with occupation defined as "other" (including laboratory/diagnostic staff and pharmacists) who declared they would not be willing to be screened for TB (13.6%) was higher than that of physicians and nurses (2.7% and 4.5% respectively).

Do you think all tuberculosis patients should be isolated for treatment?

Of those who answered the question (527 HCWs), 336 (63.8%) declared that they thought that all TB patients should be isolated for treatment. Some HCWs (21, 4%) declared that they did not know the answer to this question, while 170 (32.3%) thought that not all TB patients should be isolated. There was a clear difference in the answer to this question by occupation.

While 53.7% of physician thought that not all TB patients should be isolated, 69.6% of nurses and 75.2% of those with occupation defined as “other” thought they should. Of the HCWs who declared that they deal with TB patients during their non-Hajj work (n= 257), 65.3% provided the wrong answer to the question.

It is ok to allow a tuberculosis patient to leave the hospital soon after initiating appropriate treatment?

Of those who answered the question (521 HCWs), 254 (48.8%) declared that they thought it was ok to allow a TB patient to leave the hospital soon after initiating appropriate treatment. Some HCWs (44, 8.4%) declared that they did not know the answer to this question, while 223 (42.8%) thought that it was not ok to allow a TB patient to leave the hospital soon after initiating appropriate treatment. Nurses were more often in agreement with the statement than doctors (54.4% vs 44.8%). Of the HCWs who declared that they deal with TB patients during their non-Hajj work (n= 253), more than half (51.3%) disagreed with the above statement.

Would you be willing to attend seminars on tuberculosis?

Of those who answered the question (512 HCWs), most, 487 (95.1%), declared that they would you be willing to attend seminars on TB.

Would you recommend the suspension of treatment if a tuberculosis patient is feeling better?

Of those who answered the question (518 HCWs), 411 (79.3%) declared that they would not recommend the suspension of treatment if a TB patient was feeling better, while 46 (8.9%) reported that this question was not applicable to them. Some HCWs however (61, 11.8%) declared that they would recommend the suspension of treatment if a TB patient was feeling better. Around 6% of physicians would recommend suspension of TB treatment compared to 15.3% of nurses.

Would you start tuberculosis treatment for a tuberculosis patient before diagnosis is confirmed if a suspected tuberculosis patient is very ill?

Of those who answered the question (515 HCWs), 287 (55.7%) declared that they would not start TB treatment for a TB patient before diagnosis was confirmed if a suspected TB patient was very ill, while 43 (8.3%) reported that this question was not applicable to them. Some HCWs however (185, 35.9%) declared that they would start TB treatment for a TB patient before diagnosis was confirmed if a suspected TB patient was very ill. Among doctors, 53.7% declared they would start TB treatment before diagnosis is confirmed.

Would you use a face mask when dealing with a pulmonary tuberculosis patient even when it is uncomfortable?

Of those who answered the question (521 HCWs), 428 (82.1%) declared that they would use a face mask when dealing with a PTB patient even when it is uncomfortable, while 93 (17.9%) reported that they would not. More doctors than nurses indicated that they would use a face mask even when it is uncomfortable (85.6% vs 79.2%). Of the HCWs who declared that they deal with TB patients during their non-Hajj work (n= 253), 20.5% disagreed with the above statement.

Would you trust the result the laboratory provides you on sputum cultures?

Of those who answered the question (524 HCWs), 448 (85.5%) declared that they would trust the result the laboratory provides them on sputum cultures, while 30 (5.7%) reported that this question was not applicable to them. Some HCWs however (46, 8.8%) declared that they would not trust the result the laboratory provides them on sputum cultures. The proportion of those who indicated they trust the laboratory results was comparable across occupations.

I would not accept to examine/treat tuberculosis patients

Of those who answered the question (510 HCWs), 435 (85.3%) declared that they would accept to examine/treat TB patients, while 75 (14.7%) reported that they would not be willing to do so. The lowest proportion of HCWs who declared they would not be willing to examine TB patients was among physicians (11.6%) followed by nurses (14.5%).

I have a very low risk of acquiring tuberculosis from my patients

HCWs were asked if they thought they had very low risk of acquiring TB from their patients. Of those who answered the question (517 HCWs), 253 (48.9%) declared that they thought they did not have very low risk of acquiring TB from their patients, while 155 (30%) thought they had very low risk of acquiring TB from their patients. Around 20% of HCWs (109) declared that they did not know the answer to this question. The highest proportion of HCWs who thought they did not have a very low risk of acquiring TB from their patients were physicians (53.7%) and nurses (48.8%). Among those who declared that they thought they had very low risk of acquiring TB from their patients, 51.3% were nurses and 30.2% were doctors.

I worry about acquiring active tuberculosis disease while at work

HCWs were asked if they worried about acquiring active TB disease while at work. Of those who answered the question (510 HCWs), 350 (68.6%) declared that they worried about acquiring active TB disease while at work, while 160 (31.4%) did not worry. The proportion of HCWs who were worried about acquiring active TB while at work was higher among those who declared that they deal with TB patients during their non-Hajj work compared to those who did not (72% vs 64%).

Would you be willing to teach patients and co-workers about tuberculosis prevention?

Of those who answered the question (513 HCWs), most, 480 (93.6%) declared that they would be willing to teach patients and co-workers about TB prevention.

Would you be willing to teach patient how to collect sputum sample?

Of those who answered the question (510 HCWs), 447 (87.6%) declared that they would be willing to teach patient how to collect sputum sample, while 63 (12.4%) reported that they would not be willing to do so.

Table 36. Summary statistics of healthcare workers' attitude towards tuberculosis

Attitude statement/question	Category	Freq	%
1. Would you be willing to work in a TB clinic/ward?			
	No	309	59.31
	Yes	212	40.69
2. Would you resign from work if you are posted to a TB clinic/ward?			
	No	433	84.08
	Yes	82	15.92
3. Would you be willing to be screened for TB if you had suggestive symptoms?			
	No	29	5.66
	Yes	483	94.34
4. Do you think all TB patients should be isolated for treatment?			
	No	170	32.26
	Yes	336	63.76
	Don't know	21	3.98
5. It is ok to allow a TB patient to leave the hospital soon after initiating appropriate treatment?			
	No	223	42.8
	Yes	254	48.75
	Don't know	44	8.45
6. Would you be willing to attend seminars on TB?			
	No	25	4.88
	Yes	487	95.12
7. Would you recommend the suspension of treatment if a TB patient is feeling better?			
	No	411	79.34
	Yes	61	11.78
	NA	46	8.88
8. Would you start TB treatment for a TB patient before diagnosis is confirmed if a suspected TB patient is very ill?			
	No	287	55.73
	Yes	185	35.92
	NA	43	8.35
9. Would you use a face mask when dealing with a PTB patient even when it is uncomfortable?			
	No	93	17.85
	Yes	428	82.15
10. Would you trust the result the laboratory provides you on sputum cultures?			
	No	46	8.78
	Yes	448	85.5
	NA	30	5.73

Cont. Table 36. Summary statistics of healthcare workers' attitude towards tuberculosis

Attitude statement/question	Category	Freq	%
11. I would not accept to examine/treat a TB patients			
	No	435	85.29
	Yes	75	14.71
12. I have a very low risk of acquiring TB from my patients			
	No	253	48.94
	Yes	155	29.98
	Don't know	109	21.08
13. I worry about acquiring active TB disease while at work			
	No	160	31.37
	Yes	350	68.63
14. Would you be willing to teach patients and co-workers about TB prevention?			
	No	33	6.43
	Yes	480	93.57
15. Would you be willing to teach patient how to collect sputum sample?			
	No	63	12.35
	Yes	447	87.65

NA: not applicable, TB; tuberculosis, PTB; pulmonary tuberculosis, Freq; frequency

4.6.2 Attitude section scores

Mean scores for each attitude question/statement (min 0, max 1) are presented in Table 37.

Table 37. Mean attitude scores for healthcare workers regarding tuberculosis and its management

Attitude statement /question	N	Min	Max	Mean	SD
Would you be willing to work in a TB clinic/ward?	521	0	1	0.41	0.49
Would you resign from work if you are posted to a TB clinic/ward?	515	0	1	0.84	0.37
Would you be willing to be screened for TB if you had suggestive symptoms?	512	0	1	0.94	0.23
Do you think all TB patients should be isolated for treatment?	527	0	1	0.66	0.47
It is ok to allow a TB patient to leave the hospital soon after initiating appropriate treatment?	521	0	1	0.53	0.50
Would you be willing to attend seminars on TB?	512	0	1	0.95	0.22
Would you recommend the suspension of treatment if a TB patient is feeling better?	518	0	1	0.87	0.34
Would you start TB treatment for a TB patient before diagnosis is confirmed if a suspected TB patient is very ill?	515	0	1	0.61	0.49
Would you use a face mask when dealing with a PTB patient even when it is uncomfortable?	521	0	1	0.82	0.38
Would you trust the result the laboratory provides you on sputum cultures?	524	0	1	0.91	0.29
I would not accept to examine/treat TB patients	510	0	1	0.85	0.35

TB=tuberculosis, PTB=pulmonary tuberculosis, Min=minimum, Max, maximum, SD=standard deviation, N=number of observations

4.7 Tuberculosis practice among healthcare workers

Information on HCWs' practice regarding TB and its management was collected from answers to the following 13 statements:

1. I usually perform hand hygiene and wear PPE before contact with PTB patient/TB samples
2. I usually wear N95 respirator when caring for patient with PTB/working on TB samples
3. I request sputum tests when I suspect active TB
4. Always put the patient with active TB in the isolated room
5. I open windows when possible in TB patient rooms to increase natural ventilation
6. I order HIV test when I diagnose active TB
7. Always put the patient with known TB separated from HIV patients
8. Sometimes I use wet or soiled N95 respirator
9. I always make sure that samples are sputum and not saliva before sending them to laboratory/before testing in the laboratory
10. I commence anti-TB drugs on suspect TB cases before lab confirmation
11. I request contact tracing for all confirmed TB cases
12. I request liver function tests before starting anti-TB treatment
13. I start contacts of active TB cases who are positive for IGRA/TST tests on INH /RIF prophylaxis

4.7.1 Individual practice statements

Results of response to practice statements are summarised in Table 38.

I usually perform hand hygiene and wear personal protective equipment before contact with pulmonary tuberculosis patient/tuberculosis samples

Of those who answered the question (519 HCWs), 453 (87.3%) declared that they usually perform hand hygiene and wear PPE before contact with PTB patient/TB samples, while 27 (5.2%) reported that this question was not applicable to them. Some HCWs however (39, 7.5%) declared that they don't usually perform hand hygiene and wear PPE before contact with PTB patient/TB samples.

I usually wear N95 respirator when caring for patient with pulmonary tuberculosis /working on tuberculosis sample

Of those who answered the question (514 HCWs), 400 (77.8%) declared that they usually wear N95 respirator when caring for patient with PTB/working on TB samples, while 34 (6.6%) reported that this question was not applicable to them. Some HCWs however (80, 15.6%) declared that they don't usually wear N95 respirator when caring for patient with PTB/working on TB samples. Nurses had the highest proportion of right practice (84.9%) followed by physicians and those with occupation defined as "other", 70.5% and 69.1% respectively.

I request sputum tests when I suspect active tuberculosis

Of those who answered the question (516 HCWs), 445 (86.2%) declared that they request sputum tests when they suspect active TB, while 38 (7.4%) reported that this question was not applicable to them. Some HCWs however (33, 6.4%) declared that they don't request sputum tests when they suspect active TB. The wrong practice was more common among physicians (8.2%) compared to nurses (5.2%).

Always put the patient with active tuberculosis in the isolated room

Of those who answered the question (511 HCWs), 433 (84.7%) declared that they always put the patient with active TB in the isolated room, while 43 (8.4%) reported that this question was not applicable to them. Some HCWs however (35, 6.8%) declared that they don't always put the patient with active TB in the isolated room. The proportion of nurses who stated that they always isolate active TB patients was higher than that among physicians (90.5% vs 82.7%).

I open windows when possible in tuberculosis patient rooms to increase natural ventilation

Of those who answered the question (511 HCWs), 219 (42.9%) declared that they open windows when possible in TB patient rooms to increase natural ventilation, while 63 (12.3%) reported that this question was not applicable to them. A sizable proportion of HCWs however (229, 44.8%) declared that they don't open windows when possible in TB patient rooms to increase natural ventilation. The practice of opening the windows for ventilation was more common among doctors (45.5%) than nurses (38.9%).

I order human immunodeficiency virus test when I diagnose active tuberculosis

Of those who answered the question (513 HCWs), 319 (62.2%) declared that they order HIV test when they diagnose active TB, while 81 (15.8%) reported that this question was not applicable to them. A sizable proportion of HCWs however (113, 22.0%) declared that they don't order HIV test when they diagnose active TB. The latter practice was more common among nurses (28.1%) compared to doctors (17.0%) and HCWs with occupation as "other (14.9%).

Always put the patient with known tuberculosis separated from human immunodeficiency virus patient

Of those who answered the question (522 HCWs), 432 (82.8%) declared that they always put the patient with known TB separated from HIV patient, while 48 (9.2%) reported that this question was not applicable to them. Some HCWs however (42, 8.0%) declared that they don't always put the patient with known TB separated from HIV patient. More physicians than nurses (10.1% vs 6.6%) declared that they don't always put TB patients separate from HIV patients.

Sometimes I use wet or soiled N95 respirator

Of those who answered the question (519 HCWs), 401 (77.3%) declared that they don't use wet or soiled N95 respirator, while 64 (12.3%) reported that this question was not applicable to them. Some HCWs however (54, 10.4%) declared that sometimes they use wet or soiled N95 respirator. This was especially common among doctors (15.5%) compared to other HCWs.

I always make sure that samples are sputum and not saliva before sending them to laboratory/before testing in the laboratory

Of those who answered the question (519 HCWs), 408 (78.6%) declared that they always make sure that samples are sputum and not saliva before sending them to laboratory/before testing in the laboratory, while 65 (12.5%) reported that this question was not applicable to them. Some HCWs however (46, 8.9%) declared that they don't always make sure that samples are sputum and not saliva before sending them to laboratory/before testing in the laboratory.

I commence anti- tuberculosis drugs on suspect tuberculosis cases before lab confirmation

Of those who answered the question (522 HCWs), 302 (57.9%) declared that they do not commence anti-TB drugs on suspect TB cases before lab confirmation, while 68 (13.0%) reported that this question was not applicable to them. Some HCWs however (152, 29.1%) declared that they commence anti-TB drugs on suspect TB cases before lab confirmation including 28.3% of doctors.

I request contact tracing for all confirmed tuberculosis cases

Of those who answered the question (515 HCWs), 391 (75.9%) declared that they request contact tracing for all confirmed TB cases, while 70 (13.6%) reported that this question was not applicable to them. Some HCWs however (54, 10.5%) declared that they do not request contact tracing for all confirmed TB cases. Wrong practice was more prevalent among nurses (12.2%) than doctors (8.7%).

I request liver function tests before starting anti- tuberculosis treatment

Of those who answered the question (523 HCWs), 412 (78.8%) declared that they request liver function tests before starting anti-TB treatment, while 69 (13.2%) reported that this question was not applicable to them. Some HCWs however (42, 8.0%) declared that they do not request liver function tests before starting anti-TB treatment including 4% of physicians.

I start contacts of active tuberculosis cases who are positive for tuberculin skin test /interferon-gamma release assay tests on Isoniazid /Rifampicin prophylaxis

Of those who answered the question (516 HCWs), 317 (61.4%) declared that they start contacts of active TB cases who are positive for IGRA/TST tests on INH/RIF prophylaxis, while 114 (22.1%) reported that this question was not applicable to them. Some HCWs however (85, 16.5%) declared that they do not start contacts of active TB cases who are positive for IGRA/TST tests on INH/RIF prophylaxis. The latter practice was more common among physicians than nurses (16.9% vs 14.3%).

Table 38. Summary statistics of healthcare workers' practice regarding tuberculosis and its management

Practice statement	Category	Freq	%
1. I usually perform hand hygiene and wear PPE before contact with PTB patient/TB samples			
	No	39	7.51
	Yes	453	87.28
	NA	27	5.20
2. I usually wear N95 respirator when caring for patient with PTB/working on TB samples			
	No	80	15.56
	Yes	400	77.82
	NA	34	6.61
3. I request sputum tests when I suspect active TB			
	No	33	6.40
	Yes	445	86.24
	NA	38	7.36
4. Always put the patient with active TB in the isolated room			
	No	35	6.85
	Yes	433	84.74
	NA	43	8.41
5. I open windows when possible in TB patient rooms to increase natural ventilation			
	No	229	44.81
	Yes	219	42.86
	NA	63	12.33
6. I order HIV test when I diagnose active TB			
	No	113	22.03
	Yes	319	62.18
7. Always put the patient with known TB separated from HIV patients			
	No	42	8.05
	Yes	432	82.76
	NA	48	9.20

Cont. Table 38. Summary statistics of healthcare workers' practice regarding tuberculosis and its management

Practice statement	Category	Freq	%
8. Sometimes I use wet or soiled N95 respirator			
	No	401	77.26
	Yes	54	10.40
	NA	64	12.33
9. I always make sure that samples are sputum and not saliva before sending them to laboratory/before testing in the laboratory			
	No	46	8.86
	Yes	408	78.61
	NA	65	12.52
10. I commence anti-TB drugs on suspect TB cases before lab confirmation			
	No	302	57.85
	Yes	152	29.12
	NA	68	13.03
11. I request contact tracing for all confirmed TB cases			
	No	54	10.49
	Yes	391	75.92
	NA	70	13.59
12. I request liver function tests before starting anti-TB treatment			
	No	42	8.03
	Yes	412	78.78
	NA	69	13.19
13. I start contacts of active TB cases who are positive for IGRA/TST tests on INH /RIF prophylaxis			
	No	85	16.47
	Yes	317	61.43
	NA	114	22.09

NA: not applicable, TB; tuberculosis, PTB; pulmonary tuberculosis, HIV; human immunodeficiency virus, PPE; personal protective equipment, TST; tuberculin skin tests (TST), IGRA; interferon gamma release assay, INH; isoniazid, RIF; rifampicin, Freq; frequency

4.7.2 Practice section scores

Mean scores for each practice statement (min 0, max 1) are presented in Table 39.

Table 39. Mean practice scores for healthcare workers regarding tuberculosis and its management

Practice statement	N	Min	Max	Mean	SD
I usually perform hand hygiene and wear PPE	519	0	1	0.92	0.27
I usually wear N95 respirator when caring for patient with PTB/working on TB samples	514	0	1	0.83	0.37
I request sputum tests when I suspect active TB	516	0	1	0.93	0.25
Always put the patient with active TB in the isolated room	511	0	1	0.93	0.26
I open windows when possible in TB patient rooms to increase natural ventilation	511	0	1	0.49	0.50
I order HIV test when I diagnose active TB	513	0	1	0.74	0.44
Always put the patient with known TB separated from HIV patients	522	0	1	0.91	0.28
Sometimes I use wet or soiled N95 respirator	519	0	1	0.88	0.32
I always make sure that samples are sputum and not saliva before sending them to laboratory/before testing in the laboratory	519	0	1	0.90	0.30
I commence anti-TB drugs on suspect TB cases before lab confirmation	522	0	1	0.67	0.47
I request contact tracing for all confirmed TB cases	515	0	1	0.88	0.33
I request liver function tests before starting anti-TB treatment	523	0	1	0.91	0.29
I start contacts of active TB cases who are positive for IGRA/TST tests on INH/RIF prophylaxis	516	0	1	0.79	0.41

TB; tuberculosis, PTB; pulmonary tuberculosis, HIV; human immunodeficiency virus, PPE; personal protective equipment, TST: tuberculin skin tests (TST), IGRA; interferon gamma release assay, INH; isoniazid, RIF; rifampicin, Min; minimum, Max, maximum, SD; standard deviation, N; number of observations

4.8 Overall mean knowledge, attitude and practice scores

The mean overall KAP scores among HCWs regarding TB and its management are summarized in Table 40. The results suggest that in general HCWs had average knowledge (mean score >0.4-0.6), above average attitude (mean score >0.6-0.8) and good practice (mean score .0.8-1) in relation to TB and its management. The proportion of HCWs in each scale category are summarized in Table 41. Most HCWs had average or above average knowledge scores. On the other hand, most had above average or good attitude or practice scores.

Table 40. Overall knowledge, attitude and practice scores for healthcare workers regarding tuberculosis and its management

Score	Min	Lower Quartile	Upper Quartile	Max	Median	Mean	SD
Knowledge	0.02	0.42	0.63	0.90	0.54	0.52	0.17
Attitude	0.00	0.64	0.82	1.00	0.73	0.73	0.15
Practice	0.00	0.75	0.92	1.00	0.85	0.81	0.17

Min; minimum, Max, maximum, SD; standard deviation

Table 41. Levels of knowledge, attitude and practice of healthcare workers in relation to tuberculosis and its management

Category (mean score)	% poor (0-0.2)	% below average (>0.2-0.4)	% average (>0.4-0.6)	% above average (>0.6-0.8)	% good (>0.8-1)
Knowledge (N=540)	4.6	17.4	43.9	31.9	2.2
Attitude (N=533)	0.6	3.9	10.9	43.0	41.7
Practice (N=519)	1.0	3.3	5.6	27.4	62.8

N; number of observations

4.9 Knowledge, attitude and practice scores and demographic variables

4.9.1 Knowledge of tuberculosis and its management and demographic variables

The difference in knowledge scores with respect to individual covariates is shown in Table 42. Females had marginally significantly more knowledge than males (mean scores 0.53 vs 0.50 respectively, p= 0.04). Non-Saudi national had significantly more knowledge than Saudi nationals (mean scores 0.61 vs 0.44 respectively, p <0.0001). However, it is worth noting that a higher proportion of non-Saudi HCWs were physicians compared to Saudi HCWs (48.8% vs 13.9% respectively) and a higher proportion had a master or higher education level compared to Saudi HCWs (32.4% vs 5.37% respectively). In general, the majority of non-Saudi HCWs had a bachelor degree as the highest level of education (60.2%), while most of Saudi HCWs had a diploma as the highest level of education (57.8%).

Knowledge scores were also significantly different according to age, level of education and occupation (p <0.0001). HCWs in the older age groups had a higher knowledge score than those in the younger age groups (Figure22). Specifically, HCWs in the 40-49 year age group had significantly (p<0.0001) more knowledge than those in the 30-39 years or <30 years age groups. Also, HCWs in the age >49 years had significantly (p = 0.0008) more knowledge than those in the <30 years group. Physicians had significantly more knowledge than nurses (<0.0001) and other HCWs (<0.0001), while nurses had significantly more knowledge than HCWs other than physicians (p<0.0001) (Figure 23).

In general, HCWs with master or higher level of education had more knowledge than those with Bachelor or diploma (Figure 24). HCWs with a diploma were significantly less knowledgeable than those with Bachelor (p<0.0001), those with master (p<0.0001) and those with doctorate or specialty certificates (p<00001). The latter were also significantly more knowledgeable than HCWs with Bachelor degree (p= 0.02).

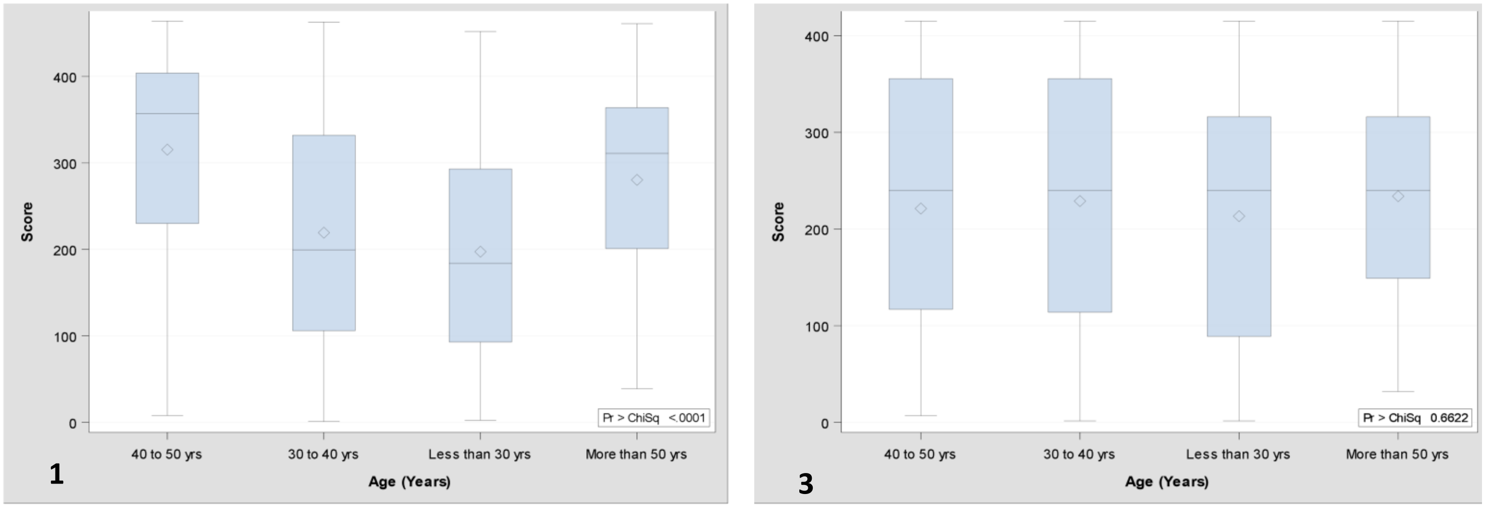
Knowledge scores were significantly different depending on length of experience in the current position ($p= 0.0029$), although this was mainly driven by the significant difference in knowledge between HCWs who had <10 years work experience compared to those who had 1-5 years work experience ($p= 0.0017$) (Figure 25). HCWs who deal with TB patients in their non-Hajj work had slightly higher mean knowledge score compared to those who do not (0.54 vs 0.50) but the difference was not statistically significant ($p= 0.07$).

Table 42. Overall tuberculosis knowledge score and the healthcare workers' demographic variables

Variable		N	Min	Mean	Max	SD	P-value*
Age							<0.0001
	<30	158	0.02	0.48	0.79	0.16	
	30-39	190	0.02	0.51	0.88	0.17	
	40-49	71	0.12	0.62	0.90	0.13	
	>49	45	0.25	0.58	0.86	0.13	
Gender							0.0461
	Female	277	0.02	0.53	0.83	0.14	
	Male	258	0.02	0.50	0.90	0.18	
Nationality							<0.0001
	Saudi	246	0.02	0.44	0.84	0.15	
	Non-Saudi	226	0.02	0.61	0.90	0.12	
Education Level							<0.0001
	Diploma	191	0.02	0.43	0.74	0.15	
	Bachelor	237	0.02	0.55	0.90	0.15	
	Master	53	0.23	0.59	0.84	0.11	
	Doctorate/Specialty certificate	40	0.13	0.62	0.86	0.16	
Occupation							<0.0001
	Other	102	0.02	0.40	0.72	0.15	
	Physician	154	0.11	0.59	0.9	0.16	
	Nurse	275	0.02	0.51	0.82	0.15	
Current position length							0.0029
	<1 year	30	0.08	0.50	0.83	0.16	
	1 - 5 years	177	0.02	0.50	0.88	0.15	
	>5 - 10 years	169	0.06	0.51	0.87	0.17	
	>10 years	145	0.11	0.56	0.90	0.15	
Non-Hajj TB patient contact							0.0749
	No	249	0.02	0.50	0.88	0.17	
	Yes	261	0.10	0.54	0.90	0.15	
Attended a TB seminar in the previous year							0.1942
	No	394	0.02	0.51	0.90	0.17	
	Yes	129	0.14	0.53	0.79	0.14	

*p-value for the Mann–Whitney U or Kruskal-Wallis test

N; number of observations, Min; minimum, Max; maximum, SD; standard deviation, TB; tuberculosis



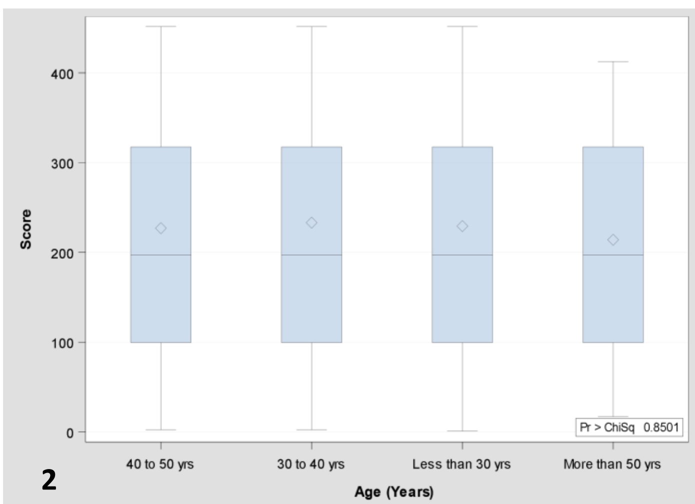
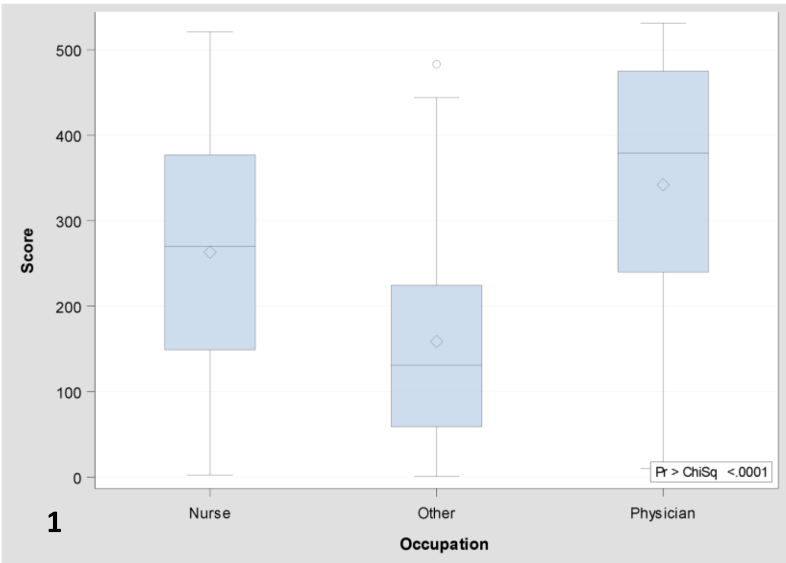
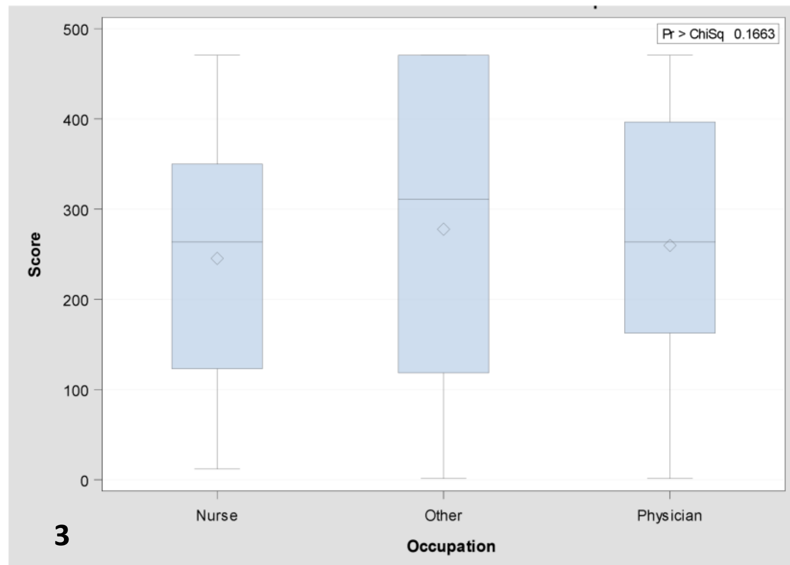


Figure 22.

Wilcoxon Scores (Rank Sums) for knowledge (1), attitude (2) and practice (3) scores classified by healthcare workers' age groups





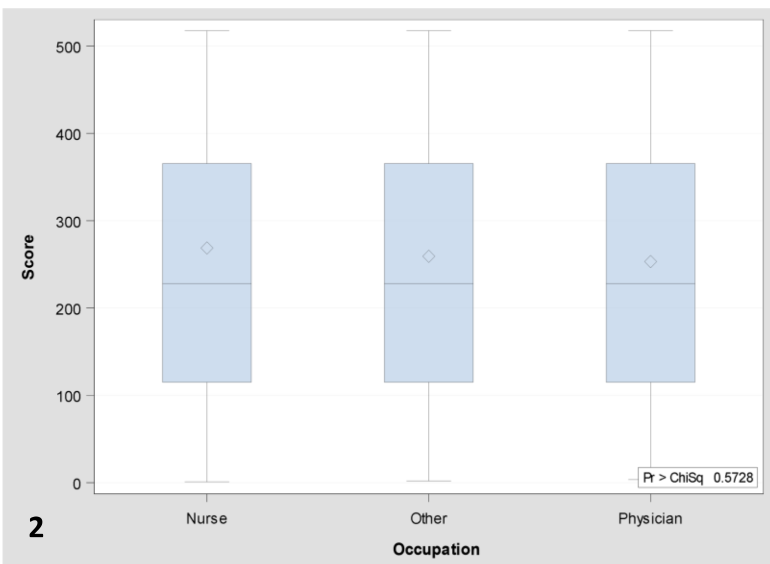
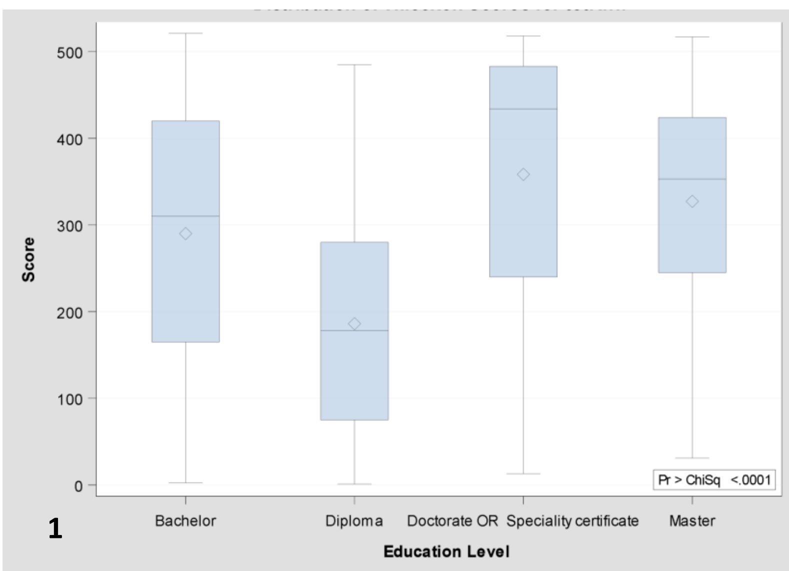
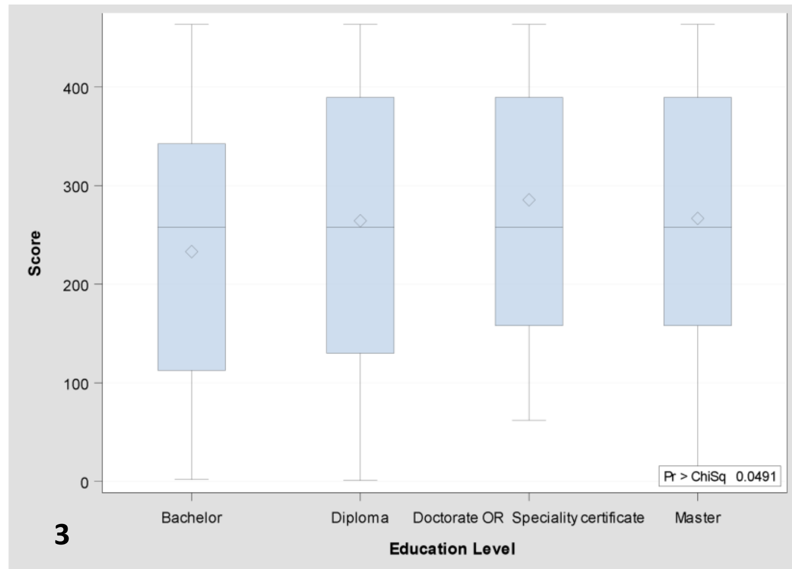


Figure 23. Wilcoxon Scores (Rank Sums) for knowledge (1), attitude (2) and practice (3) scores classified by healthcare workers' occupation





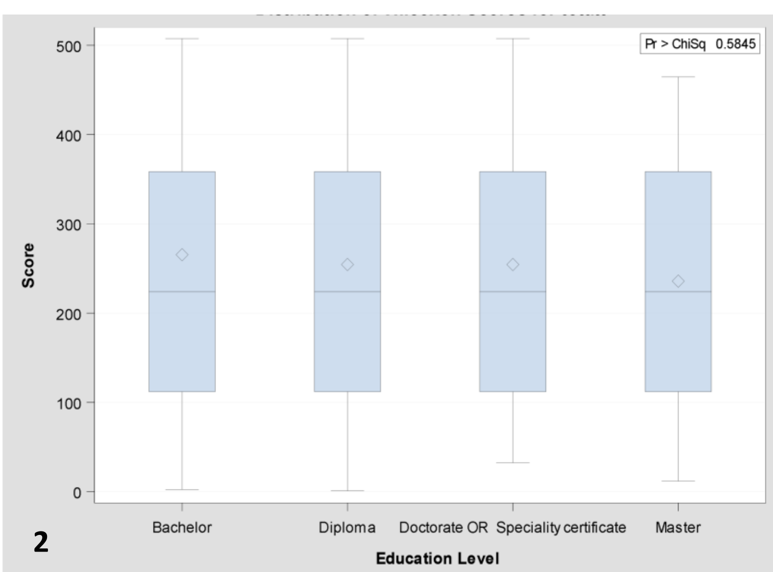
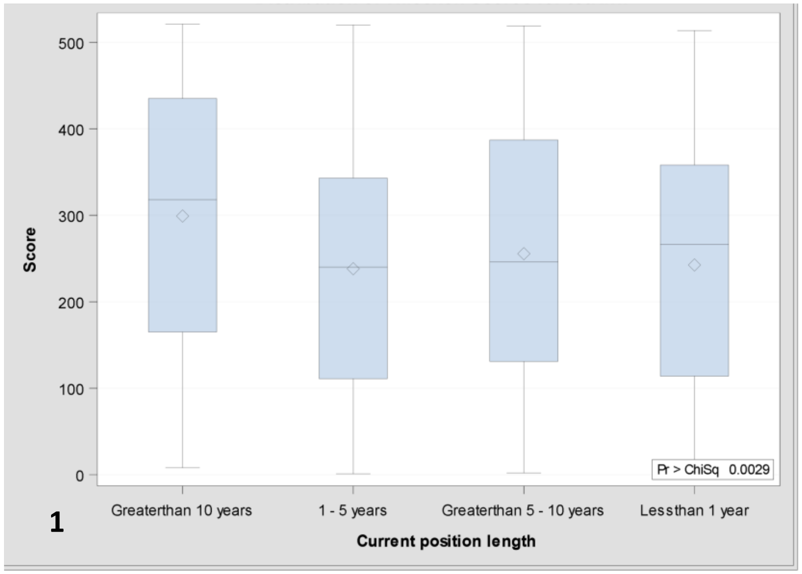
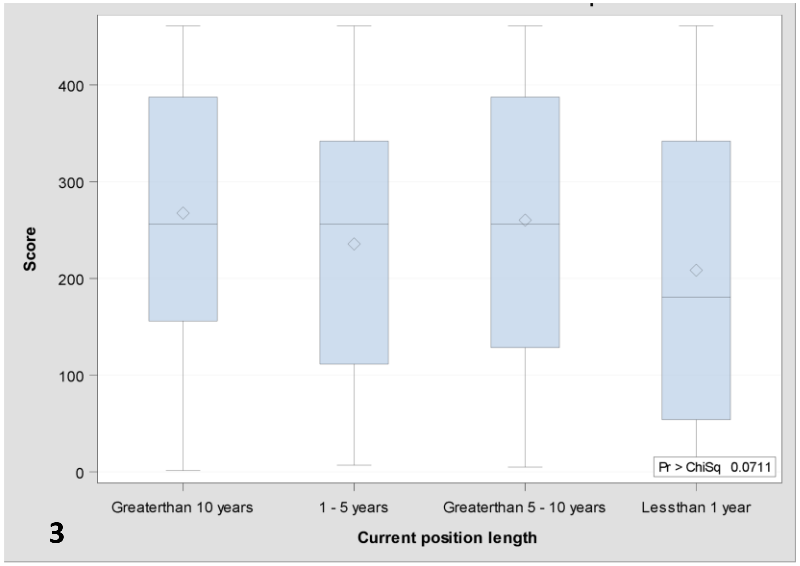


Figure 24. Wilcoxon Scores (Rank Sums) for knowledge (1), attitude (2) and practice (3) scores classified by healthcare workers' level of education





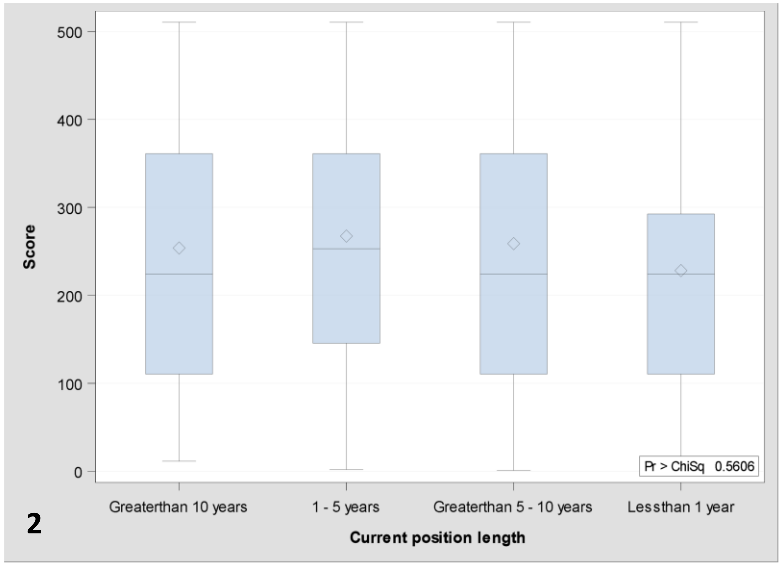


Figure 25. Wilcoxon Scores (Rank Sums) for knowledge (1), attitude (2) and practice (3) scores classified by healthcare workers' length of work experience

4.9.2 Attitude towards tuberculosis and its management and demographic variables

The difference in attitude scores with respect to individual covariates is shown in Table 43. The overall attitude scores did not statistically significantly differ in relation to demographic variables.

Table 43. Overall tuberculosis attitude score and the healthcare workers' demographic variables

Variable		N	Min	Mean	Max	SD	P-value*
Age							0.8501
	<30	158	0.00	0.73	1.00	0.15	
	30-39	190	0.20	0.73	1.00	0.16	
	40-49	71	0.20	0.73	1.00	0.15	
	>49	45	0.36	0.72	0.91	0.13	
Gender							0.0667
	Female	277	0.00	0.74	1.00	0.13	
	Male	258	0.20	0.71	1.00	0.16	
Nationality							0.1623
	Saudi	246	0.00	0.72	1.00	0.16	
	Non-Saudi	226	0.27	0.75	1.00	0.14	
Education Level							0.5845
	Diploma	191	0.00	0.72	1.00	0.16	
	Bachelor	237	0.20	0.74	1.00	0.15	
	Master	53	0.33	0.72	0.91	0.12	
	Doctorate/Specialty certificate	40	0.45	0.74	1.00	0.12	
Occupation							0.5728
	Other	102	0.20	0.72	1.00	0.18	
	Physician	154	0.25	0.72	1.00	0.13	
	Nurse	275	0.00	0.74	1.00	0.15	
Current position length							0.5606
	<1 year	30	0.25	0.71	1.00	0.17	
	1 - 5 years	177	0.20	0.74	1.00	0.14	
	>5 - 10 years	169	0.00	0.73	1.00	0.16	
	>10 years	145	0.30	0.73	1.00	0.13	
Non-Hajj TB patient contact							0.1914
	No	249	0.00	0.72	1.00	0.16	
	Yes	261	0.25	0.74	1.00	0.13	
Attended a TB seminar in the previous year							
	No	394	0.00	0.73	1.00	0.15	0.8862
	Yes	129	0.27	0.73	1.00	0.14	

*p-value for the Mann–Whitney U or Kruskal-Wallis test; N; number of observations, Min; minimum, Max; maximum, SD; standard deviation, TB; tuberculosis

4.9.3 Tuberculosis practice and demographic variables

The difference in practice scores with respect to individual covariates is shown in Table 44. Level of education was the only variable that showed marginally statistically significant difference (p=0.04). While HCWs with doctorate or specialty certifications had slightly better practice comparted to other HCWs (Figure 24), pairwise analysis did not show significant difference among the groups. Similarly, although there were differences in practice depending on age, occupation and years of experience (Figures 22, 23, 25), these differences were not significant in the pairwise analysis.

Table 44. Overall tuberculosis practice score and the healthcare workers' demographic variables

Variable		N	Min	Mean	Max	SD	P-value*
Age							0.6622
	<30	158	0.00	0.79	1.00	0.17	
	30-39	190	0.00	0.80	1.00	0.19	
	40-49	71	0.23	0.80	1.00	0.16	
	>49	45	0.54	0.83	1.00	0.10	
Gender							0.1404
	Female	277	0.11	0.81	1.00	0.18	
	Male	258	0.00	0.80	1.00	0.20	
Nationality							0.3412
	Saudi	246	0.00	0.79	1.00	0.20	
	Non-Saudi	226	0.22	0.80	1.00	0.13	
Education Level							0.0491
	Diploma	191	0.00	0.81	1.00	0.19	
	Bachelor	237	0.11	0.79	1.00	0.15	
	Master	53	0.22	0.82	1.00	0.16	
	Doctorate/Specialty certificate	40	0.63	0.86	1.00	0.10	
Occupation							0.1663
	Other	102	0.00	0.80	1.00	0.23	
	Physician	154	0.00	0.81	1.00	0.17	
	Nurse	275	0.27	0.80	1.00	0.14	

Cont. Table 44. Overall tuberculosis practice score and the healthcare workers' demographic variables

Variable		N	Min	Mean	Max	SD	P-value*
Current position length							0.0711
	<1 year	30	0.00	0.72	1.00	0.27	
	1 - 5 years	177	0.25	0.79	1.00	0.16	
	>5 - 10 years	169	0.22	0.82	1.00	0.15	
	>10 years	145	0.00	0.83	1.00	0.14	
Non-Hajj TB patient contact							0.3053
	No	249	0.00	0.81	1.00	0.17	
	Yes	261	0.00	0.80	1.00	0.16	
Attended a TB seminar in the previous year							
	No	394	0.00	0.80	1.00	0.17	0.1473
	Yes	129	0.11	0.82	1.00	0.17	

*p-value for the Mann–Whitney U or Kruskal-Wallis test

N; number of observations, Min; minimum, Max; maximum, SD; standard deviation, TB; tuberculosis

4.9.4 Quantile regression

Due to the data being skewed, quantile regression was used to investigate the association between variables and the overall KAP scores across the different score levels (Figures 26-28). Results of quantile regression are presented for the 25th, 50th and 75th quantiles for the scores (Tables 45-53) and summarized in Table 54. The reference groups used were: male, >49 years old, Saudi national, physician, <1 year in current position and having contact with TB patients in non-Hajj work.

4.9.4.1 Tuberculosis knowledge

Results of quantile regression at the 25th, 50th, and 75th knowledge score quantiles show that all age groups had more knowledge than the reference group, but the regression coefficient was significant only for the 40-49 years old group and only at the 50th quantiles. Females were more knowledgeable than males and the regression coefficient was significant at the 25th and 50th quantiles (Tables 45, 46).

Non-Saudis had better knowledge than Saudis and this was significant at all three quantiles. Physicians were more knowledgeable than both nurses and other HCWs. This was significant at the three quantiles for other HCWs but only at the higher quantiles (50th and 75th) for nurses (Tables 46, 47). HCWs with <1 year in their current position were less knowledgeable than those who had longer experience at all quantiles, but the regression coefficient was only significant for those with >10 years work experience. HCWs who had contact with TB patients during their non-Hajj work had more knowledge than those who did not at all three quantiles. The regression coefficient was however only statistically significant at the lowest quantile (25th).

Results of quantile regressing across quantiles (Figure 26) show that compared to HCWs >49 years old, HCWs in other age groups were more knowledgeable across all quantiles. The regression coefficient was not statistically significant across all quantiles for HCWs in the <30 years old and 30-39 years old groups. For those aged between 40 and 49 years old, the regression coefficient seems to be significant at most of the lower and middle knowledge score quantiles but not the higher quantiles. Females were more knowledgeable than males across all quantiles. However, the regression coefficient seems to be only significant at few of the low and middle quantiles. Non-Saudis were more knowledgeable than Saudis across all quantiles and the regression coefficient was also significant across all quantiles. Physicians were more knowledgeable than nurses or other HCWs across all quantiles with the exception for nurses at the lowest quantiles. The regression coefficient was statistically significant across all quantiles for “other” HCWs. For nurses, the regression coefficient was significant at some of the lower quantiles and at the higher quantiles. Compared to HCWs with <1 year work experience, other HCWs were more knowledgeable across all quantiles with the exception of those with 1-5 years and 5-10 years work experience which were less knowledgeable at the lowest quantiles. The regression coefficients were not significant across most quantiles with the exception of some middle quantiles for all categories and higher quantiles for the >10 years group. HCWs with TB-patients contact were more knowable than those who do not deal with TB patients in their work, and this was evident across all quantiles. The regression coefficient was however only significant at the lower half of the knowledge score quantiles.

4.9.4.2 Tuberculosis attitude

Results of quantile regression at the 25th, 50th, and 75th attitude score quantiles show that for age groups, HCWs in the 30-39 years and 40-49 years old had better attitude than those >49 years old but the regression coefficient was only significant at the 75th quantile for the 30-39 years old age group (Table 50). At the 50th quantile, HCWs <30 years old had worst attitude than those >49 years old with no significant regression coefficient (Table 49). Females and non-Saudis had better attitude compared to males and Saudis respectively but the regression coefficient was not significant at any of the three quantiles. Similarly, nurses and other HCWs had better attitude than physicians across the three quantiles. The regression coefficient was however only significant at the 50th quantile for "other" HCWs (Table 49). HCWs with <1 year work experience had worst attitude compared to other HCWs at the three quantiles with no significant regression coefficient. HCWs who deal with TB patient had better attitude at the 25th quantile than those who do not but the regression coefficient was not significant (Table 48).

Results of quantile regressing across all attitude score quantiles (Figure27) show that all age groups had better attitude than the reference group across all quantiles with the exception of the age group <30 years old which showed worst attitude at some of the middle attitude score quantiles. The regression coefficients were not significant with the exception of some of the high quantiles for the 30-39 age group. Females had better attitude than males across quantiles but the regression coefficient was only significant at some of the lowest quantiles. Non-Saudis had better attitude than Saudis across all quantiles with regression coefficients significant at some low and very high quantiles. Nurses and other HCWs had better attitude than physicians but this was not the case at the lowest quantiles. Regression coefficients were mostly not significant with the exception of some high and middle quantiles. Compared to HCWs with <1 year work experience other HCWs had better attitude, with the exception of highest quantiles. Regression coefficients were not significant with the exception of at some high quantiles. HCWs with TB-patients contact had better attitude than those who do not deal with TB patients in their work mainly at the low quantiles with the regression coefficient being significant at the lowest quantiles.

4.9.4.3 Tuberculosis practice

Results of quantile regression at the 25th, 50th, and 75th practice score quantiles show that at the 25th and 75th quantiles, compared to HCWs >49 years old, those <30 years old had worst practice while those 30-39 years and 40-49 years old had better practice. However, the regression coefficients were not significant (Tables 51, 53). Females had better practice than males with no significant regression coefficients. Non-Saudis had better practice than Saudis at the 25th quantile (Table 51) but worst practice at the 75th quantile (Table 53) with no statistically significant regression coefficients. Similarly, "other" HCWs had worst practice compared to physicians at the 25th quantile (Table 51) but better practice at the 50th and 75th quantiles (Tables 52, 53). The regression coefficient at the latter quantile was statistically significant. Nurses had worst practice than physicians at the 25th and 75th quantiles with no significant regression coefficients (Tables 51, 53). HCWs with <1 year work experience had worst practice compared to other HCWs at the three quantiles with no significant regression coefficient. HCWs with no contact with TB patients had better practice at the 25th and 75th quantiles compared to those who have contact with TB patients, but the regression coefficients were not significant (Tables 51, 53).

Results of quantile regressing across all practice score quantiles (Figure 28) show that all age groups had better practice than the reference group across most quantiles. However, at most quantiles between the 60th and 80th practice score quantiles, the reference group had better practice. The regression coefficients were not significant for any age group at any quantile. Females had better practice than males across most quantiles with the exception of some lower quantiles with no significant regression coefficients. Non-Saudis had better practice than Saudis at low quantiles but worst practice at higher quantiles. The regression coefficients were significant at some higher quantiles. Physicians had better practice than nurses across quantiles with no significant regression coefficients. However, physicians had better practice than "other" HCWs only at lower quantiles.

At higher quantiles, "other" HCWs had better practice compared to physicians with regression coefficients being significant at higher end of the quantiles range. Compared to HCWs with <1 year work experience other HCWs had better practice across most quantiles, with the exception of at the highest quantiles. Regression coefficients were not significant with the exception of at some lower quantiles (around the 20th quantile) for all groups and at some higher quantiles for HCWs with >10 years experience. HCWs with TB-patients contact had worst practice than those who do not deal with TB patients in their work with no significant regression coefficients.

Table 45. Association between variables and overall knowledge score of healthcare workers at the 25th quantile

Variable		Coef	95% CI		p-value
Intercept		0.363	0.2763	0.4498	<.0001
Age					
	<30	0.0069	-0.0747	0.0885	0.8682
	30-39	0.0192	-0.0548	0.0933	0.6095
	40-49	0.0708	0.0015	0.14	0.0452
Gender					
	Female	0.0452	0.0066	0.0838	0.022
Nationality					
	Non-Saudi	0.145	0.1106	0.1794	<.0001
Occupation					
	Other	-0.1112	-0.183	-0.0394	0.0025
	Nurse	-0.039	-0.0872	0.0092	0.1126
Current position length					
	1 - 5 years	0.0388	-0.0265	0.104	0.2438
	>5 - 10 years	0.0397	-0.0302	0.1097	0.2646
	>10 years	0.0764	0.0092	0.1436	0.0259
Non-Hajj TB patient contact					
	No	-0.0616	-0.0965	-0.0267	0.0006

Coef; regression coefficient, CI; confidence interval, TB; tuberculosis

p-value in bold indicates statistically significant p-value

Table 46. Association between variables and overall knowledge scoreof healthcare workers at the 50th quantile

Variable		Coef	95% CI		p-value
Intercept		0.4413	0.3629	0.5197	<.0001
Age					
	<30	0.0017	-0.0625	0.0659	0.9585
	30-39	0.0116	-0.0417	0.0648	0.6693
	40-49	0.0699	0.0318	0.108	0.0004
Gender					
	Female	0.0381	0.0007	0.0754	0.0457
Nationality					
	Non-Saudi	0.1065	0.0748	0.1383	<.0001
Occupation					
	Other	-0.1056	-0.1651	-0.0462	0.0005
	Nurse	-0.0455	-0.0881	-0.0029	0.0365
Current position length					
	1 - 5 years	0.0591	-0.012	0.1302	0.1028
	>5 - 10 years	0.066	-0.0021	0.1341	0.0573
	>10 years	0.0756	0.0118	0.1394	0.0203
Non-Hajj TB patient contact					
	No	-0.0146	-0.0397	0.0105	0.2543

Coef; regression coefficient, CI; confidence interval, TB; tuberculosis

p-value in bold indicates statistically significant p-value

Table 47. Association between variables and overall knowledge score of healthcare workers at the 75th quantile

Variable		Coef	95% CI		p-value
Intercept		0.5711	0.4684	0.6737	<.0001
Age					
	<30	0.0125	-0.0469	0.0718	0.6804
	30-39	0.0277	-0.0256	0.0811	0.3069
	40-49	0.0383	-0.0254	0.1021	0.2381
Gender					
	Female	0.0277	-0.0178	0.0732	0.2323
Nationality					
	Non-Saudi	0.0804	0.0439	0.1168	<.0001
Occupation					
	Other	-0.1585	-0.2252	-0.0919	<.0001
	Nurse	-0.0977	-0.1532	-0.0421	0.0006
Current position length					
	1 - 5 years	0.0601	-0.0062	0.1265	0.0757
	>5 - 10 years	0.0653	-0.0011	0.1317	0.054
	>10 years	0.0891	0.0107	0.1674	0.026
Non-Hajj TB patient contact					
	No	-0.0135	-0.0405	0.0134	0.3247

Coef; regression coefficient, CI; confidence interval, TB; tuberculosis

p-value in bold indicates statistically significant p-value

Table 48. Association between variables and overall attitude score of healthcare workers at the 25th quantile

Variable		Coef	95% CI		p-value
Intercept		0.5758	0.4593	0.6923	<.0001
Age					
	<30	0	-0.0934	0.0934	1
	30-39	0.0303	-0.0508	0.1114	0.4632
	40-49	0	-0.0871	0.0871	1
Gender					
	Female	0.0333	-0.0148	0.0814	0.1738
Nationality					
	Non-Saudi	0.0303	-0.009	0.0696	0.1304
Occupation					
	Other	0	-0.0775	0.0775	1
	Nurse	0.0273	-0.0362	0.0908	0.3988
Current position length					
	1 - 5 years	0.0606	-0.0309	0.1521	0.1937
	>5 - 10 years	0.0303	-0.0694	0.13	0.5504
	>10 years	0.0606	-0.0377	0.1589	0.2263
Non-Hajj TB patient contact					
	No	-0.0303	-0.0665	0.0059	0.1006

Coef; regression coefficient, CI; confidence interval, TB; tuberculosis

p-value in bold indicates statistically significant p-value

Table 49. Association between variables and overall attitude score of healthcare workers at the 50th quantile

Variable		Coef	95% CI		p-value
Intercept		0.6862	0.5788	0.7936	<.0001
Age					
	<30	-0.016	-0.0899	0.0579	0.6702
	30-39	0.0225	-0.0375	0.0826	0.4614
	40-49	0.0216	-0.0413	0.0845	0.4999
Gender					
	Female	0.0219	-0.026	0.0697	0.3692
Nationality					
	Non-Saudi	0.0352	-0.0078	0.0783	0.1084
Occupation					
	Other	0.0684	0.0075	0.1293	0.0279
	Nurse	0.0298	-0.0274	0.0871	0.3061
Current position length					
	1 - 5 years	0.0578	-0.0188	0.1343	0.1388
	>5 - 10 years	0.0054	-0.0775	0.0883	0.898
	>10 years	0.0058	-0.0751	0.0868	0.8871
Non-Hajj TB patient contact					
	No	0	-0.0325	0.0325	1

Coef; regression coefficient, CI; confidence interval, TB; tuberculosis

p-value in bold indicates statistically significant p-value

Table 50. Association between variables and overall attitude score of healthcare workers at the 75th quantile

Variable		Coef	95% CI		p-value
Intercept		0.7596	0.6649	0.8542	<.0001
Age					
	<30	0	-0.0657	0.0657	1
	30-39	0.0707	0.0142	0.1273	0.0144
	40-49	0	-0.0429	0.0429	1
Gender					
	Female	0	-0.0357	0.0357	1
Nationality					
	Non-Saudi	0.0202	-0.0166	0.057	0.2815
Occupation					
	Other	0.0202	-0.0361	0.0765	0.4808
	Nurse	0.0202	-0.0266	0.067	0.3969
Current position length					
	1 - 5 years	0.0384	-0.0244	0.1012	0.2304
	>5 - 10 years	0.0384	-0.0271	0.1039	0.2501
	>10 years	0.0384	-0.0317	0.1085	0.2823
Non-Hajj TB patient contact					
	No	0	-0.0227	0.0227	1

Coef; regression coefficient, CI; confidence interval, TB; tuberculosis

p-value in bold indicates statistically significant p-value

Table 51. Association between variables and overall practice score of healthcare workers at the 25th quantile

Variable		Coef	95% CI		p-value
Intercept		0.5974	0.4065	0.7882	<.0001
Age					
	<30	-0.0037	-0.1246	0.1173	0.9525
	30-39	0.0067	-0.0899	0.1032	0.8923
	40-49	0.0009	-0.0951	0.0969	0.9856
Gender					
	Female	0.0067	-0.0544	0.0677	0.8304
Nationality					
	Non-Saudi	0.0143	-0.05	0.0786	0.6611
Occupation					
	Other	-0.0187	-0.1231	0.0857	0.725
	Nurse	-0.025	-0.0991	0.0491	0.5073
Current position length					
	1 - 5 years	0.1067	-0.0342	0.2475	0.1373
	>5 - 10 years	0.117	-0.0247	0.2586	0.1053
	>10 years	0.1567	0.0014	0.3119	0.0479
Non-Hajj TB patient contact					
	No	0.0183	-0.0247	0.0614	0.4021

Coef; regression coefficient, CI; confidence interval, TB; tuberculosis

p-value in bold indicates statistically significant p-value

Table 52. Association between variables and overall practice score of healthcare workers at the 50th quantile

Variable		Coef	95% CI		p-value
Intercept		0.7778	0.663	0.8926	<.0001
Age					
	<30	0	-0.0706	0.0706	1
	30-39	0	-0.0542	0.0542	1
	40-49	0	-0.0627	0.0627	1
Gender					
	Female	0	-0.045	0.045	1
Nationality					
	Non-Saudi	0	-0.0368	0.0368	1
Occupation					
	Other	0.0128	-0.0509	0.0765	0.6925
	Nurse	0	-0.0457	0.0457	1
Current position length					
	1 - 5 years	0.0684	-0.0237	0.1604	0.1448
	>5 - 10 years	0.0556	-0.0429	0.154	0.2679
	>10 years	0.0684	-0.0324	0.1692	0.1831
Non-Hajj TB patient contact					
	No	0	-0.0275	0.0275	1

Coef; regression coefficient, CI; confidence interval, TB; tuberculosis

p-value in bold indicates statistically significant p-value

Table 53. Association between variables and overall practice score of healthcare workers at the 75th quantile

Variable		Coef	95% CI		p-value
Intercept		0.8594	0.774	0.9448	<.0001
Age					
	<30	-0.0002	-0.0533	0.0529	0.9933
	30-39	0.0064	-0.0419	0.0548	0.7945
	40-49	0	-0.0442	0.0442	1
Gender					
	Female	0.0002	-0.0296	0.0301	0.9881
Nationality					
	Non-Saudi	-0.0066	-0.0411	0.0278	0.7053
Occupation					
	Other	0.0639	0.0068	0.1209	0.0282
	Nurse	-0.0066	-0.0418	0.0285	0.7105
Current position length					
	1 - 5 years	0.0629	-0.0063	0.1322	0.0747
	>5 - 10 years	0.0639	-0.0024	0.1301	0.0587
	>10 years	0.0639	0	0.1277	0.050
Non-Hajj TB patient contact					
	No	0.0064	-0.0157	0.0285	0.5694

Coef; regression coefficient, CI; confidence interval, TB; tuberculosis

p-value in bold indicates statistically significant p-value

Table 54. Summary of the association between variables and overall scores of healthcare workers at the 25th, 50th and 75th quantiles

Variable		**Coef for knowledge scores (SE)**			**Coef for attitude scores (SE)**			**Coef for practice scores (SE)**		
		25th	**50th**	**75th**	**25th**	**50th**	**75th**	**25th**	**50th**	**75th**
Intercept		**0.363**	**0.4413**	**0.5711**	**0.5758**	**0.6862**	**0.7596**	**0.5974**	**0.7778**	**0.8594**
		(0.050)	(0.041)	(0.060)	(0.059)	(0.050)	(0.051)	(0.087)	(0.052)	(0.045)
Age										
	<30	0.0069	0.0017	0.0125	0.000	-0.016	0.000	-0.0037	0.000	-0.0002
		(0.045)	(0.029)	(0.033)	(0.041)	(0.037)	(0.039)	(0.058)	(0.033)	(0.023)
	30-39	0.0192	0.0116	0.0277	0.0303	0.0225	**0.0707**	0.0067	0.000	0.0064
		(0.038)	(0.041)	(0.029)	(0.038)	(0.032)	(0.033)	(0.053)	(0.030)	(0.021)
	40-49	0.0708	**0.0699**	0.0383	0.000	0.0216	0.000	0.0009	0.000	0.000
		(0.034)	(0.020)	(0.033)	(0.042)	(0.028)	(0.023)	(0.045)	(0.029)	(0.018)
Gender										
	Female	**0.0452**	**0.0381**	0.0277	0.0333	0.0219	0.000	0.0067	0.000	0.0002
		(0.017)	(0.018)	(0.024)	(0.026)	(0.023)	(0.019)	(0.034)	(0.022)	(0.015)
Nationality										
	Non-Saudi	**0.145**	**0.1065**	**0.0804**	0.0303	0.0352	0.0202	0.0143*	0.000*	-0.0066*
		(0.018)	(0.014)	(0.018)	(0.022)	(0.020)	(0.019)	(0.029)	(0.018)	(0.016)

Cont. Table 54. Summary of the association between variables and overall scores of healthcare workers at the 25th, 50th and 75th quantiles

Variable		Coef for knowledge scores (SE)			Coef for attitude scores (SE)			Coef for practice scores (SE)		
		25th	50th	75th	25th	50th	75th	25th	50th	75th
Occupation										
	Other	**-0.1112**	**-0.1056**	**-0.1585**	0.000	**0.0684**	0.0202	-0.0187*	0.0128*	**0.0639***
		(0.036)	(0.029)	(0.033)	(0.038)	(0.030)	(0.027)	(0.052)	(0.032)	(0.020)
	Nurse	-0.039	**-0.0455**	**-0.0977**	0.0273	0.0298	0.027)	-0.025	0.000	-0.0066
		(0.023)	(0.020)	(0.027)	(0.030)	(0.024)	(0.020)	(0.039)	(0.022)	(0.018)
Current position length										
	1 - 5 years	0.0388	0.0591	0.0601	0.0606	0.0578	0.0384	0.1067	0.0684	0.0629
		(0.033)	(0.033)	(0.032)	(0.048)	(0.037)	(0.030)	(0.068)	(0.042)	(0.035)
	>5 - 10 years	0.0397	0.066	0.0653	0.0303	0.0054	0.0384	0.117	0.0556	0.0639
		(0.037)	(0.032)	(0.035)	(0.051)	(0.040)	(0.034)	(0.069)	(0.044)	(0.035)
	>10 years	**0.0764**	**0.0756**	**0.0891**	0.0606	0.0058	0.0384	**0.1567**	0.0684	0.0639
		(0.037)	(0.033)	(0.044)	(0.052)	(0.040)	(0.038)	(0.075)	(0.044)	(0.035)
Non-Hajj TB patient contact										
	No	**-0.0616**	-0.0146	-0.0135	-0.0303	0.000	0.000	0.0183	0.000	0.0064

Figure 26. Estimations of the regression coefficient and 95% confidence intervals (shaded area) for each quantile of the healthcare workers' knowledge scores

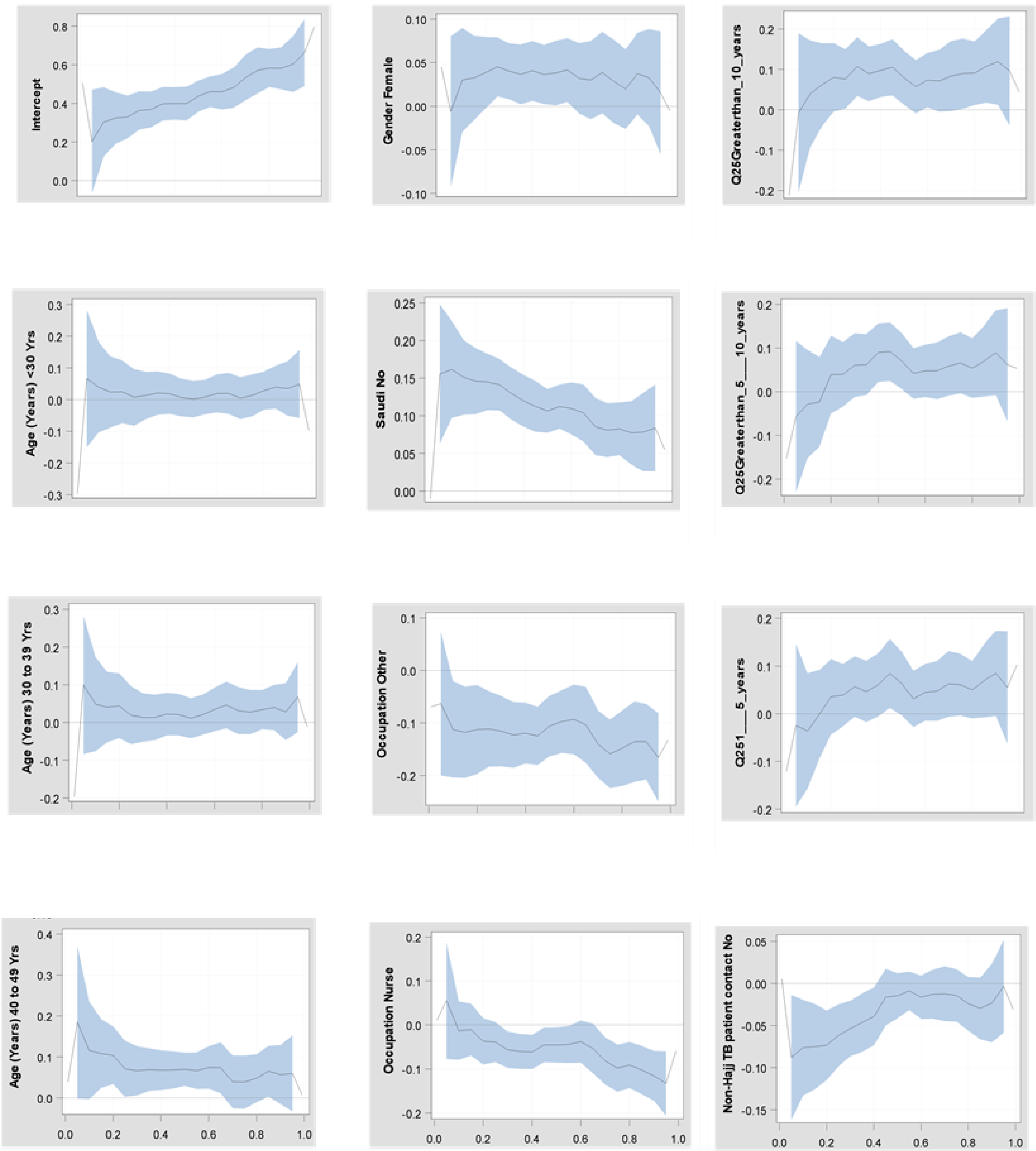


Figure 27. Estimations of the regression coefficient and 95% confidence intervals (shaded area) for each quantile of the healthcare workers' attitude scores

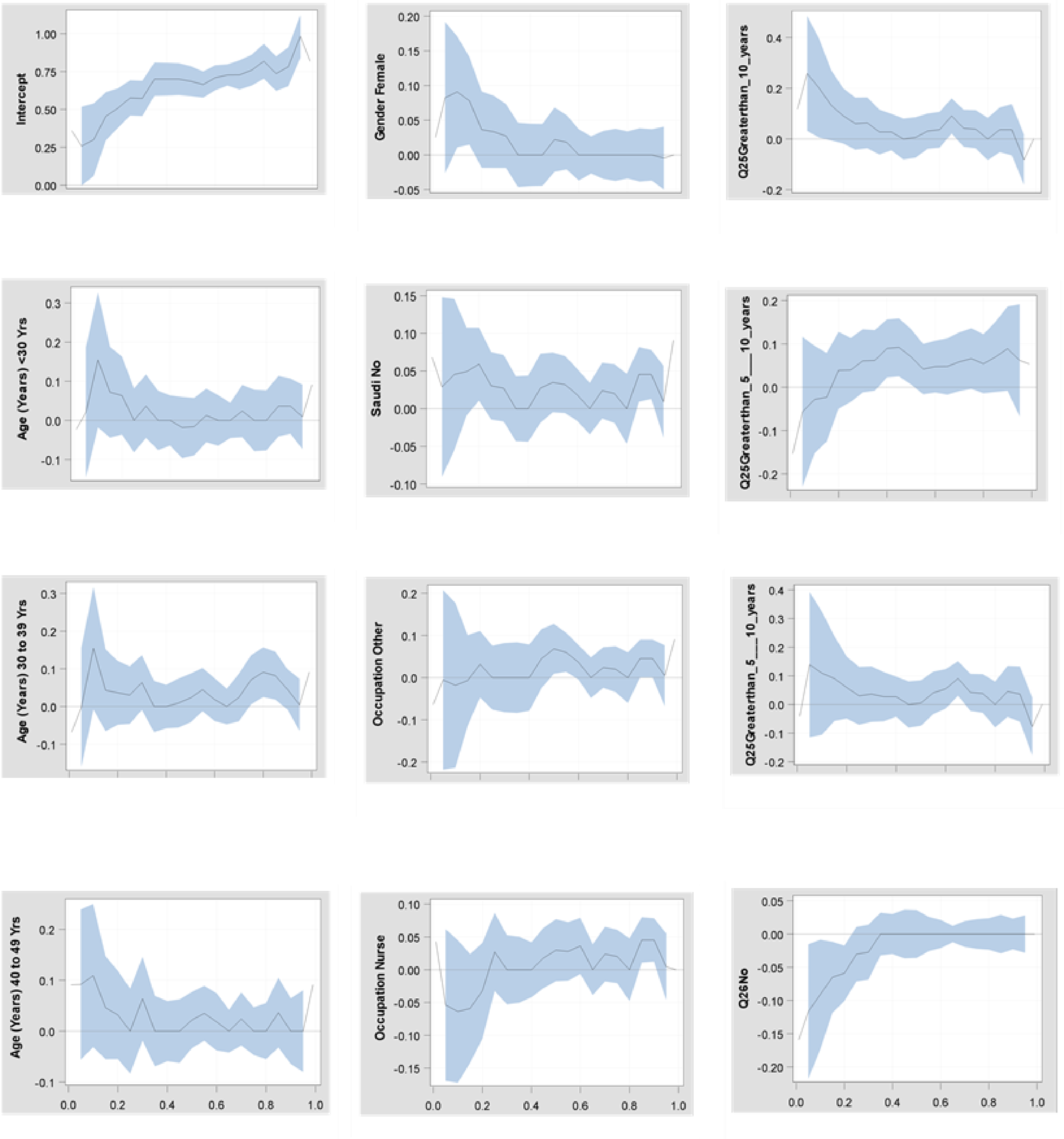
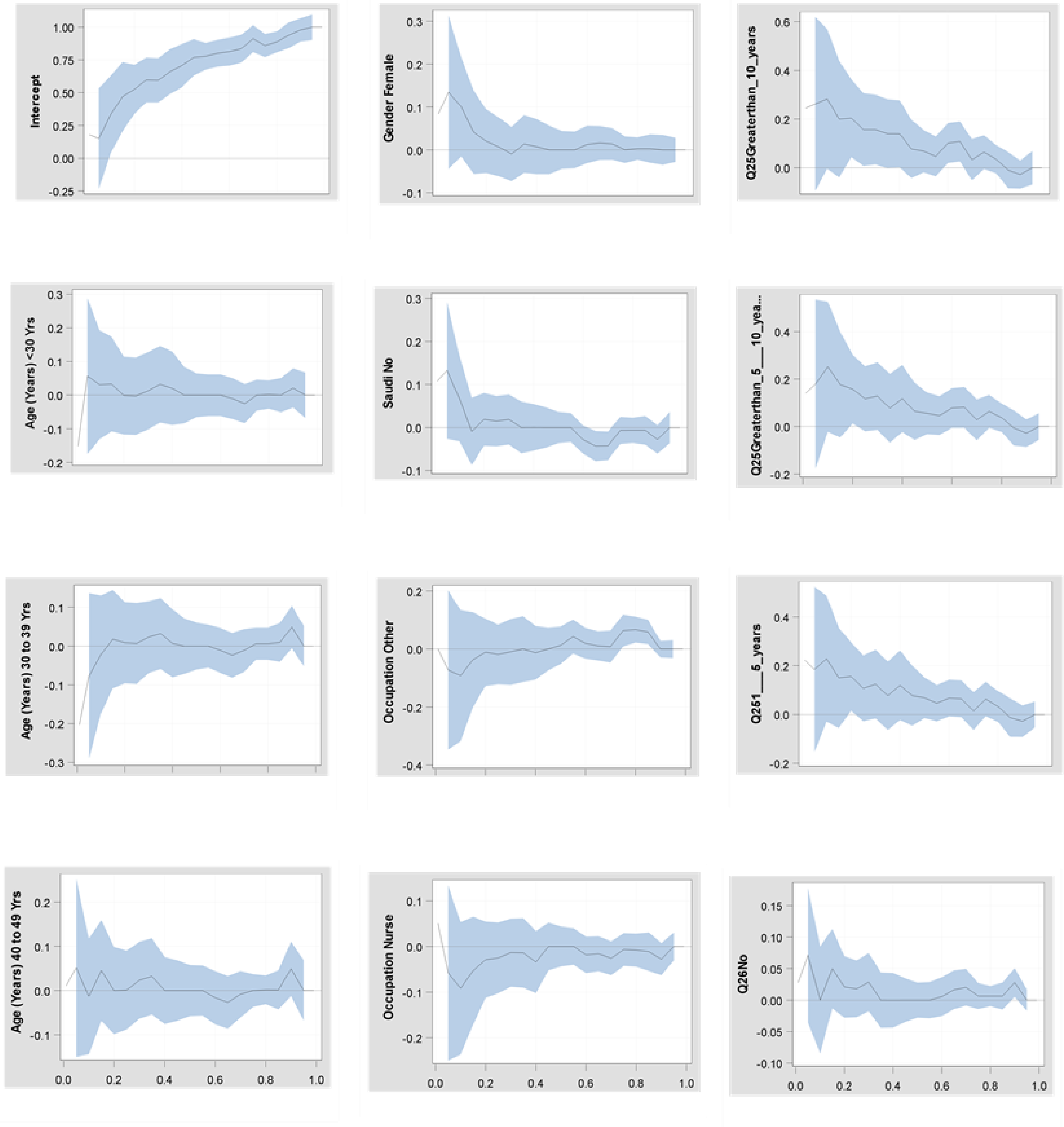


Figure 28. Estimations of the regression coefficient and 95% confidence intervals (shaded area) for each quantile of the healthcare workers' practice scores



4.9.5 Correlations between tuberculosis knowledge attitude and practice among healthcare workers

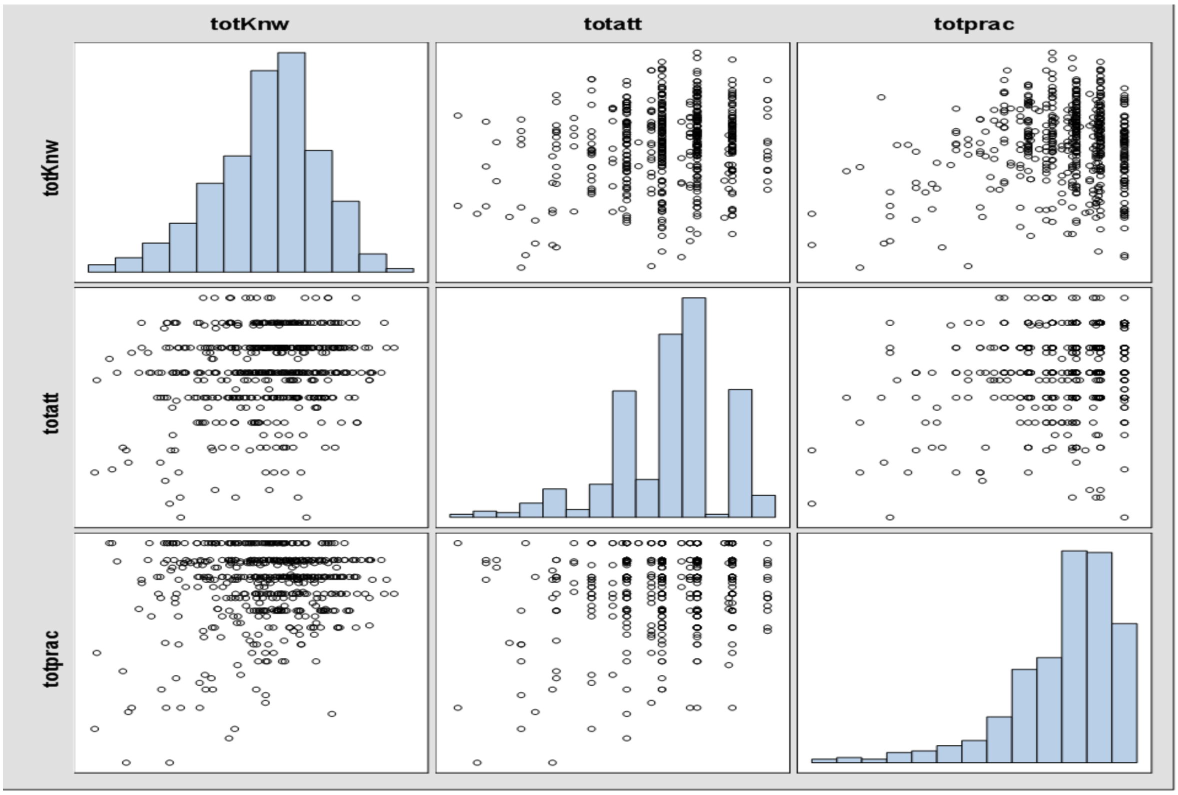
Figure 29 and Table 55 show that there is a weak but statistically significant positive correlation between knowledge and attitude (r_s=0.11) and attitude and practice (r_s=0.13).

Table 55. Correlations between tuberculosis knowledge attitude and practice scores for healthcare workers

Correlation variable	N	Spearman correlation coefficient	p-value
Knowledge vs attitude	518	0.11362	0.0096*
Knowledge vs practice	518	-0.0101	0.818
Attitude vs practice	518	0.13142	0.0027*

*statistically significant N, number of observations

Figure 29. Scattered plot matrix representing the correlation between total knowledge (totKnw), total attitude (totatt) and total practice (totprac) scores



4.10 Discussion

The current study conducted the first KAP survey regarding TB among HCWs serving during the Hajj. The results of this investigation have already been published (Alotaibi et al., 2019).

4.10.1 Knowledge of tuberculosis among healthcare workers

Knowledge maybe defined as "what people know about certain subjects or as information that is acquired or gained" (Wahab et al., 2016). We evaluated knowledge of HCWs regarding TB and its management across four general themes: nature of the disease (epidemiology and microbiology), diagnosis, treatment and infection prevention and control. We found that the mean overall knowledge score (0.52) fell within the average range (0.4-0.6). Most HCWs were deemed to have either average or above average knowledge, 43.9% and 31.9% respectively. According to our scale, only a small proportion of HCWs (2.2%) were found to have good knowledge. Various studies from around the word investigated knowledge of HCWs regarding TB and found varying results. Some reported poor knowledge(Noe et al., 2017, Shrestha et al., 2017, Woith et al., 2010), and others found adequate (Buregyeya et al., 2016, Minnery et al., 2013) or good knowledge (Bhebhe et al., 2014, Hashim et al., 2003). However, interpretation of the results of these studies and comparison with our data should be done within the context of the methodology use in each study and the scales or cut of points used for the definition of the level of knowledge. For example, reports among HCWs from Peru (Minnery et al., 2013) Mozambique(Noe et al., 2017) and Russia (Woith et al., 2010) found average knowledge scores of 67.3%, 57.3% and 51.7% respectably, which are close to what we found among HCWs working in Hajj (52%). Still the study from Mozambique concluded that HCWs knowledge regarding TB patient characteristics, diagnosis and treatment was poor(Noe et al., 2017) while that from Russia deemed the overall score to below (Woith et al., 2010).

A study from Iraq (Hashim et al., 2003) found that 95% of HCWs had “good” knowledge about TB, while another from Lesotho found 89.2% of HCWs had appropriate knowledge of transmission, diagnosis and prevention of TB. In the latter study, fair and good knowledge were defined as scores of 40-69% and >70% respectively. According to this scale, our study found similar results as 78% of HCWs in our study had a score of >40%.

In Thailand, 56% of healthcare providers were found to possess a “good” level of knowledge of TB (Lertkanokkun et al., 2013). The proportion of providers with good level of knowledge regarding the nature of disease, diagnosis, treatment and follow up were 71.2%, 37.2%, 65.1% and 55.2% respectively. In another study among health staff at basic healthcare facilities in rural Vietnam revealed that 90% of them were aware of the nature of TB disease (Hoa et al., 2005). In Uganda, 62% of HCWs were judged to have adequate basic TB knowledge based on a cut of point for knowledge score of >85 (Buregyeya et al., 2016). In Nepal, 54% of HCWs answered ≥ 60% of the knowledge questions on TB infection control correctly and were considered to have “good” level of knowledge (Shrestha et al., 2017).

In our study, none of the HCWs surveyed answered all knowledge questions correctly and only 2.2% had an overall mean knowledge score over 80%. Buregyeya et al. (Buregyeya et al., 2016) reported that 24% of HCWs from health facilities in the districts of Mukono and Wakiso in Uganda answered all TB basic knowledge questions correctly. However, it is worth noting that latter study only included 7 “yes/no” questions regarding TB basic knowledge compared to our study which had 23 questions, a number of which were multiple choice. Results reported by Bhebhe and colleagues (Bhebhe et al., 2014) were more similar to ours as they found that only 3.1% of HCWs investigated from a hospital in Lesotho received a knowledge score of ≥ 70%. In a multinational study conducted among HCWs in China, India, Iran and Mexico, only 12% of respondents correctly answered all the 5 TB knowledge questions (Hoffman et al., 2016).

4.10.1.1 Nature of tuberculosis disease (epidemiology and microbiology)

Our study identified key knowledge gaps among HCWs working during Hajj with regards to a number of aspects of TB and its treatment. In relation to the nature of the disease (epidemiology and microbiology), 25% of HCWs did not correctly identify TB as a bacterial infection and nearly 12% did not know that PTB is curable. These were slightly higher rates than those reported from other countries. Studies from Russia, Peru, Iraq, Vietnam and Lesotho found that 1-12.6% of HCWs did not know that TB was caused by a bacterium and 2.3-8% did not know that TB was curable (Bhebhe et al., 2014, Hashim et al., 2003, Hoa et al., 2005, Minnery et al., 2013, Woith et al., 2010).

Most HCWs in our study (83.6%) identified the airborne route as the mode of transmission of PTB and indicated coughing (93%) and sneezing (65%) as routes of transmission. This is in accordance with numerous other studies that reported that over 80% of HCWs are aware that TB is transmittable thought the airborne route (Bhebhe et al., 2014, Buregyeya et al., 2016, Ferreira Junior et al., 2013, Hashim et al., 2003, Minnery et al., 2013, Shrestha et al., 2017, Woith et al., 2010). However, we found that in addition to coughing and sneezing, 17-42%thought that PTB can be transmitted through sharing food or drinks, contaminated surfaces, kissing or handshaking. Such misconceptions have been reported among HCWs albeit to a lesser extent. For example, 1.8% of HCWs investigated in Iraq thought TB is transmitted thought a route other than breath (Hashim et al., 2003), while 2% of HCWs in a study from Uganda identified utensils and shaking hands as rotes of TB transmission (Buregyeya et al., 2016). In a study among public health workers in Sao Paulo, Brazil, 94.9% thought TB was transmitted thought the air, but similar misconceptions about routes of transmission found in our study were identified (Ferreira Junior et al., 2013). Nearly 40% and 24.7% respectively thought TB was transmitted thought sharing dishes/cutlery and through sharing food. Moreover, some public health workers also believed that TB was transmitted through other routes including handshaking (3.2%), saliva (1.3%), touching doorknobs (8.2%), and drug use, kissing and contaminated food (1.3%).

HCWs, especially front-line staff are an important source of information for patients due to their involvement in patient support. As such lack of knowledge regarding the ways TB is transmitted among HCWs may also explain the similar misconceptions widespread among patients. For instance, in a recent study among patients at primary healthcare facilities in South Africa, only 15.0% knew that TB cannot be transmitted through sharing toothbrushes and only 35.5% were aware that TB cannot be transmitted through kissing (Kigozi et al., 2017).

Another concerning result from our study is the lack of knowledge of HCWs regarding drug-resistant TB (MDR- and XDR-TB). Drug-resistant TB is a global health threat with significant morbidity and mortality and an important challenge to the WHO’s End TB Strategy (Marahatta, 2010, Seung et al., 2015, World Health Organization, 2017b). Only a quarter of HCWs knew the definition of MDR-TB and even a smaller proportion (12.7%) knew the definition of XDR-TB. In addition, only half of the HCWs thought MDR-TB was curable.

Although it is generally assumed HCWs know about MDR-TB and its implications, the evidence from several studies worldwide have found that HCWs do not always have sufficient knowledge of MDR-TB, even those working in TB facilities (Isara and Akpodiete, 2015, Malangu and Adebanjo, 2015, Minnery et al., 2013, Woith et al., 2010). A study among HCWs participating in the Peruvian national TB control program found that only 37.2% knew the definition of MDR-TB (Minnery et al., 2013). The proportion among medical doctors, nurses, nurse technicians, health promoters and other HCWs were 40.4%, 38.4%, 40.3%, 39.5% and 30.7%. In a study from Russia, only 59% of TB HCWs from 5 TB facilities recognised that MDR-TB was curable (Woith et al., 2010). A study among HCWs in Lesotho reported that less than half (47.3%) had good level of knowledge about MDR-TB (Malangu and Adebanjo, 2015). Although patients harboring MDR and XDR strains present a formidable challenge for treatment, cure is often possible with early identification of resistance and use of a properly designed regimen(Seung et al., 2015). Hence, it is important that HCWs, especially front-line staff, are aware of MDR-TB, able to diagnose it early and are aware of the fact that patients with MDR- and XDR-TB can be cured and communicate this information to patients and the community at large.

BCG vaccines are among the oldest vaccines first used in humans back in 1921. The BCG is a live attenuated bacterial vaccine derived from *Mycobacterium bovis* that was originally isolated in 1902 from a tuberculous cow (Luca and Mihaescu, 2013). While BCG has demonstrated significant effectiveness in several populations, protection has not been consistent against all forms of TB and in all age groups. However, there is no evidence of effectiveness when BCG is used as post-exposure prophylaxis (World Health Organization, 2018a). The WHO recommends BCG vaccination for unvaccinated TST- or IGRA-negative HCWs at risk of occupational exposure in low and high TB incidence areas (World Health Organization, 2018a). In the USA, the CDC recommends that BCG vaccination of HCWs should be considered on an individual basis in settings in which a high percentage of TB patients are infected with *M. tuberculosis* strains resistant to both INH and RIF; there is ongoing transmission of such drug-resistant strains to HCWs and subsequent infection is likely; or comprehensive TB infection-control precautions have been implemented, but have not been successful (Centers for Disease Control and Prevention, 2012).

Vaccination is also recommended in number of other countries (La Torre et al., 2017). Our results showed that there is genuine confusion among HCWs regarding the role of the BCG vaccine in the protection against TB with nearly an equal number (about a third) of HCWs thinking it is protective, not protective, or did not know the answer. This confusion is seen even among HCWs from high TB settings such as South Africa, where one study reported that among HCWs in a hospital in Lesotho, BCG vaccination was identified by 58.6% of the respondents as not being a preventive measure against contracting PTB, while the rest thought it was (Bhebhe et al., 2014).

We found that most HCWs (81%) were aware that HIV patients were more vulnerable to contracting TB. HIV patients are at increased risk of contracting TB and TB recurrence (Mirsaeidi and Sadikot, 2018). In fact, concurrent HIV infection has been reported to be the greatest single risk factor for developing TB from infection (Davies, 2005). The ability to identify individuals at risk of TB has important implication for early detection of the disease and appropriate treatment and supportive interventions as well as infection prevention and control measures. As with our results, reports from a number of countries found that in general most HCWs were aware that HIV patients are more vulnerable to TB. For example, Bhebhe et al. (Bhebhe et al., 2014) reported that 96.1% of HCWs investigated from a hospital in Lesotho thought that HIV patients are predisposed to contracting TB. Similarly, Buregyeya and colleagues (Buregyeya et al., 2016) found that 97% of HCWs from healthcare facilities in two districts in Uganda indicated that HIV infection increased the risk of developing TB. However, knowledge of other individuals at higher risk of TB apart from HIV patients may not be as high among HCWs. A number of risk factors have been identified related to increasing the risk of TB infection and active disease including diabetes, smoking, alcohol use, and the use of drugs. Silva et al (Silva et al., 2018) and Minnery et al. (Minnery et al., 2013) reported that when HCWs participating in the Peruvian national TB control program were asked to identify people at higher risk of developing TB disease from a list that included people with HIV, diabetes, chronic diseases, people in close contact with TB patients and pregnant woman, only 58.8% had a correct response. Medical doctors and nurses performed better (70% and 63% respectively), but only 42% of health promoters gave the correct answer. Our study did not investigate knowledge of HCWs regarding people at risk of TB beyond HIV patients.

4.10.1.2 Tuberculosis diagnosis

Overall, only 3.6% of HCWs in our study correctly identified all of the main symptoms of PTB given in the multiple-choice question. This is in contrast to two studies from Russia and Peru which reported around 75% of HCWs correctly identified the most common symptoms of PTB (Minnery et al., 2013, Woith et al., 2010). It is worth nothing however, that unlike our study population, the latter studies were conducted among specifically TB HCWs working in TB facilities or HCWs participating in national TB control programs, which may explain the high level of knowledge regarding TB symptoms. While the majority of HCWs (63-80%) in our study correctly identified some common symptoms of PTB such as cough ≥ 3 weeks, cough with blood, fever/chills and weight loss, confusion was apparent for other common symptoms of PTB such as tiredness and fatigue, chest pain, loss of appetite and night sweats, as only around half of the HCWs (40-57%) correctly identified these as symptoms of PTB. A proportion of HCWs (1.3-16.1%) identified symptoms not commonly associated with PTB as main symptoms of the disease including headaches, dizziness, pain when urinating, diarrhoea, memory loss and blurry vision. This gap in knowledge regarding the main symptoms of PTB was observed even among physicians although the proposition of correct answers, in general, were higher among physicians compared to other HCWs.

Numerous studies found similar results to ours. In a study from Lesotho, most HCWs were able to identify constitutional symptoms of TB (chronic cough (94.7%), night sweats (84.5%) and weight loss (79.1%) but only 53.3% cindered fever to be a symptom of TB (Bhebhe et al., 2014). A study from Nepal, found that most (67.4%) of HCWs investigated were aware of the major symptoms of TB. Cough ≥ 2 weeks, weight loss, fever, loss of appetite, chest pain and blood in sputum were identified as symptoms of TB by 67.4%, 75.3%, 85.3%, 57.9%, 67.2% and 61.6% of HCWs respectively. As with our results, the proportions of HCWs correctly identifying symptoms were generally higher among clinical staff compared to other HCWs such as laboratory, ward support or administrative staff (Shrestha et al., 2017). Among HCWs in Vietnam, persistent cough was chosen as the most frequent symptom (98%) of TB (Hoa et al., 2005).

Among public health workers in Brazil, the TB symptoms were identified as follows: 2-weeks cough (86.7%), cough with blood (56.3%), fever (39.9%), weight loss (67.7%), chest pain (30.4%) and fatigue (51.9%)(Ferreira Junior et al., 2013). Among HCWs in Iraq, 93.2% identified cough >3 weeks as a sign of TB. Fever, haemoptysis, and night sweats were identified as signs of TB by 70-76% of HCWs, while 51-60% identified loss of appetite, chest pain, loss of weight and general weakness as signs of TB (Hashim et al., 2003).

Gaps in knowledge regarding common symptoms of TB are concerning especially in the context of HCWs working during Hajj. Key factors facilitating TB transmission, both in the community and in healthcare settings, include undiagnosed TB or delays in diagnosing and treating TB patients (Golub et al., 2006, Greenaway et al., 2002, Jensen et al., 2005, Menzies et al., 2007). Undiagnosed TB, both among hospitalized and non-hospitalised Hajj pilgrims have been reported, representing a risk for TB transmission among pilgrims, local population and international spread of infection (Al-Orainey, 2013, Alzeer et al., 1998, Yezli et al., 2017b). Hence, lack of knowledge regarding symptoms of TB may translate into delays in identifying, isolating and treating patients with TB or in TB patients not being diagnosed with the disease and consequent transmission.

We found important knowledge gaps with regards to other aspects of TB diagnosis among the HCWs. Very few HCWs (1.6%) correctly identified all diagnostic tests for PTB from the list of options presented to them and only 0.2% correctly identified all the screening tests for LTBI. There was clear confusion regarding the purpose of the tests and the difference between tests to diagnose active disease and those used to screen for latent infection. For instance, 71% of HCWs identified chest X-ray as diagnostic tests for PTB. In addition, while 57-71% of HCWs identified chest X-ray, sputum culture and sputum AFB smear tests as diagnostic tests for PTB, 35-53% also identified these tests as screening tests for LTBI. Also, a smaller proportion of HCWs (60%) identified TST as a LTBI screening tests than those who thought it was a test for diagnosing PTB (65.7%). Interestingly, IGRA was identified as a LTBI screening tests and as a PTB diagnostic test in a similar but small proportion of HCWs (12.7% and 13.3% respectively). This was similar to the GeneXpert MTB/RIF test where only 12% of HCWs knew it was a diagnostic test for PTB, while 7% thought it was a screening test for LTBI. Additionally, while most HCWs correctly identified the most useful sputum collection method, only 16% knew the percentage of active PTB that would be positive on a smear microscopy.

These gaps appear not only to be related to lack of knowledge of the tests, especially modern techniques, but also to a confusion between active TB disease and LTBI. This confusion has been reported in other studies. Only 54.7% of all HCWs and 68% of clinical staff investigated from healthcare facilities in Nepal knew the difference between TB infection and disease (Shrestha et al., 2017), while a study from Uganda reported that 42% of HCWs thought there was no difference between TB infection and TB disease (Buregyeya et al., 2016). Among TB HCWs in Peru, only 54% knew that not all people infected with TB develop TB disease (Minnery et al., 2013). Lack of knowledge regarding diagnostic techniques have also been reported in various studies around the world, although in most to a lesser extent to what was found in our study. A study among HCWs in Iraq found that while 78.8% defined active PTB correctly according to the national guidelines, 19% believed that the disease could be detected only by chest X-ray (Hashim et al., 2003). In South Africa, although most (97%) HCWs investigated knew that smear examination was a major diagnostic tool for PTB, only 22% knew the appropriate place to collect sputum (Bhebhe et al., 2014). This is in contrast to a report by Hong et al.(Hong et al., 1995) which found that sputum examination was considered neglected in cause-finding among private general practitioners in Korea as more than 50% did not consider sputum examination essential in case finding/diagnosis. Hoa et al. (Hoa et al., 2005) reported that although most (89%) HCWs they surveyed in Vietnam correctly identified the most effective diagnostic tool for PTB. Around (65%) knew how many sputum samples are needed to be collected for diagnosis but only 19% reported the correct number and method of collecting these samples. Minnery et al. (Minnery et al., 2013) also reported that most HCWs in a study from Peru were aware of the number of sputum samples needed for TB diagnosis. However, a disappointing proportion (24%) correctly identified the most effective tool in diagnosing PTB from a list that contained sputum examination, chest X-ray, blood culture and TST. A study from Uganda reported that 19% of HCWs agreed that the first step in assessing a TB suspect was to send them for a chest X-ray and 94% indicated that sputum smear microscopy for AFB was the quickest and cheapest way to identify infectious TB patients (Buregyeya et al., 2016).

A striking observation in our results was the poor knowledge among HCWs regarding the use of GeneXpert MTB/RIF for TB diagnosis. Similar results were reported among HCWs in rural Mozambique, where less than 30% of those surveyed had heard of the test (Noe et al., 2017). GeneXpert MTB/RIF is a relatively new nucleic acid amplification test used for diagnosis of TB and resistance testing especially in a low-resource high-TB burden settings. It is clear that despite the WHO issuing recommendations endorsing this technology in 2010, and the widespread uptake of its use worldwide since (World Health Organization, 2014c), knowledge of its existence and purpose remains low in our study as well as in others (Noe et al., 2017). It is worth noting that GeneXpert MTB/RIF is available in the Kingdom, hence lack of knowledge among HCWs may suggest that the roll out of this technology might not have been accompanied with sufficient education for HCWs (Noe et al., 2017). Some argued that while this technology is lauded as “a major advance for TB diagnostics”, without a widespread understanding of its potential among HCWs and the critical operational requirement of trained laboratory and clinical staff, GeneXpert MTB/RIF may not be fully adopted (Piatek et al., 2013).

The use of rapid molecular diagnostic techniques for TB such as GeneXpert MTB/RIF is important in the context of Hajj given the characteristics of the pilgrims’ population, the crowded environment, the short duration of the mass gathering, and potential for international transmission. It is likely that in the future the technology will become a stable point-of-care test in healthcare facilities in the Hajj area; hence, improving HCWs knowledge regarding this test is of great importance. Lack of knowledge regarding IGRA in our study is also surprising given that the test is used in Saudi Arabia and commonly reported in studies from the Kingdom (Al Wakeel et al., 2015, Balkhy et al., 2016, 2017, Bukhary et al., 2018). Given that there is no gold standard test for LTBI (Lamberti et al., 2015), the WHO recommends either TST or IGRA to test for LTBI (World Health Organization, 2018c). The above maybe also be an indication that HCWs working during Hajj are not up-to-date regarding modern TB diagnostic and screening techniques and recent literature as well as national and international guidelines in relation to TB and LTB (Al Jahdali et al., 2010, Lamberti et al., 2015, World Health Organization, 2017b, 2018c).

4.10.1.3 Tuberculosis treatment

We identified key knowledge gaps regarding TB treatment among HCWs in our study. Overall only 6% of HCWs correctly identified all the 1^{st}-line anti-TB drugs on the survey, and even lower proportion (4.5%) identified all 2^{nd}-line anti-TB drugs. Commonly used and known drugs such as INH and RIF were better recognised than other drugs such as EMB and PZA as 1^{st}-line anti-TB treatments. For 2^{nd}-line anti-TB drugs, there was clear confusion as the proportion of HCWs who identified the various drugs as 2^{nd}-line anti-TB drugs was similar. This confusion combined with the observed lack of knowledge regarding the definitions of MDR- and XDR-TB among HCWs in our study is concerning. Also, the fact that nearly 64% of the HCWs did not know or chose a shorter duration of treatment for TB patients is also alarming. Treatment with too few drugs and for a too short duration has been shown to result in ineffective treatment outcomes of patients and an increased risk of acquiring resistance (Menzies D. et al., 2009). In addition, treatment of TB patients with fewer than four drugs in the intensive phase has been shown to result in higher percentages of relapse cases (Fox et al., 1999).

Studies on knowledge of HCWs relating to TB found that questions related to TB treatment and follow up had usually the biggest knowledge gaps. For example, a study among TB care teams from 30 hospitals in Thailand reported that the mean scores of the knowledge questions relating to TB treatment were lower than those related to either the nature of the disease of diagnosis (Lertkanokkun et al., 2013). Around 65% and 55% of the participants were deemed to have good knowledge regarding TB treatment and follow up respectively. A similar observation was reported in a study among TB HCWs in Peru where investigators found that among knowledge questions, the worst knowledge scores were seen in the TB treatment section with a total participants average of 4.2 out of 7 or 60% correct answers (Minnery et al., 2013). In the later study, HCWs were knowable regarding the number of drugs used for the treatment of PTB and the appropriate treatment duration (87.4% and 95% respectively). However, poor knowledge was observed regarding the consequences of an incomplete or abounded treatment, the most effective form for evaluating the results of a complete treatment scheme and the frequency of follow up sputum tests under the TB treatment scheme (48.8%, 35.5% and 16.9% respectively).

These results were not very different when the analysis was restricted to only medical doctors or nurses (Minnery et al., 2013). Similarly, among HCWs in rural Vietnam, around 65% knew how many drugs are used in treatment of TB, how many times follow-up sputum is carried out and the major elements to assess treatment outcome (Hoa et al., 2005). However, only 49% knew what are the consequence of inadequate/incomplete treatment. A study among TB HCWs in Russia reported that only one-third were able to identify why TB should be treated for at least 6 months, 58% understood the importance of a four-drug regime and only 43% knew the adverse reactions that may be cause by INH (Woith et al., 2010). Gaps in knowledge regarding possible side effects of INH appear to be common among HCWs from different countries. A study from 4 countries in Asia, the Middle East and South America also reported that only 45% of HCWs investigated knew the major side effects of INH therapy (Hoffman et al., 2016).

Unlike the results seen in our study where only 31% of HCWs correctly identified the appropriate treatment duration for drug-sensitive TB, many studies among HCWs worldwide reported much better knowledge. Among HCWs in studies from Lesotho, Iraq, and Vietnam, 99.2%, 87% and 65.6% correctly identified the treatment duration for TB (Bhebhe et al., 2014, Hashim et al., 2003, Hoa et al., 2005). Similarly, a study among HCWs from China, India, Iran and Mexico found that most (83%) HCWs surveyed knew the minimum duration of therapy for culture-proven active TB (Hoffman et al., 2016). In the latter study, 87% of HCWs were able to identify a TB therapy that was not a 1st-line treatment for TB. In our study, 1.3-9.5% of HCWs wrongly identified various antibiotics as 1st-line anti TB drugs. In general, available data from around the world indicate a lack of knowledge of national and international TB treatment guidelines and recommendations among HCWs.

In a systematic review reporting on 31 studies from 14 counties in Asia, America, and Africa, HCWs with inappropriate knowledge of treatment regimens (8-100%) or treatment duration (5-99%) were observed in all studies (van der Werf et al., 2012). The few studies providing detailed data showed that HCWs mainly reported giving treatment regimens with too many drugs and for too long. Knowledge of appropriate doses was also insufficient in most studies.

Such gaps in knowledge and deficiencies in practice related to TB treatment have negative implications with regards to treatment outcome as well as development of resistance. Indeed one of the greatest contributors to MDR-TB is improper treatment that may be prescribed or administered by health professionals, either because of inaccurate diagnosis, insufficient treatment supplies, or limits in their knowledge of evidence-based TB control practices (Langendam et al., 2012, Smetana et al., 2007). Despite numerous national and international guiltiness relating to the treatment of TB, including various updates of the WHO guidelines (van der Werf et al., 2012, World Health Organization, 2010c), inappropriate treatment of TB is common worldwide. In a systematic review, Langendam et al (Langendam et al., 2012) assessed the percentage of TB patients that received an inappropriate treatment regimen from 37 studies from 22 countries, and one study was from multiple countries. Almost all continents were represented. Inappropriate treatment regimens were prescribed in 67% of the studies. The percentage of patients receiving inappropriate regimens varied between 0.4% and 100%. The authors highlighted the need to improve implementation of the WHO TB treatment guidelines.

4.10.1.4 Tuberculosis infection prevention and control

Infection prevention and control in healthcare settings is one of the key strategies for TB control. The WHO recommends TB infection prevention and control in healthcare institutions based on four levels: managerial, administrative, environmental and personal protective (World Health Organization, 2009b). These measures have been found to minimize TB transmission (Basu et al., 2007, Dharmadhikari et al., 2012). However, implementation of these recommendations seems to be inadequate. Several studies have reported poor TB infection control measures in health facilities (Demissie Gizaw et al., 2015, Farley et al., 2012, He et al., 2010, Ogbonnaya et al., 2011). Further, many HCWs are practicing without adequate infection control training and often lack knowledge on TB infection control strategies (Demissie Gizaw et al., 2015, Kanjee et al., 2011, Shrestha et al., 2017, Woith et al., 2012). This is likely to contribute to the increased risk of nosocomial transmission of TB. In our study, we report good overall knowledge regarding TB infection prevention and control among HCWs, but important knowledge gaps were identified. While we found that most HCWs knew that PPE was important when dealing with TB patients and could identify the appropriate PPE to be used, nearly 5% thought PPE use was not important for their protection from TB and 18% indicated that surgical masks are appropriate PPE to use when dealing with patients with active TB. In addition, a large proportion of HCWs thought that patient with LTBI were infectious.

Respiratory protection is an important aspect of TB infection control programs and consists of the use of protective equipment in situations of a high risk for exposure to TB disease. The WHO recommends HCWs to use particulate respirators that meet or exceed the N95 standards set by the USA CDC/National Institute for Occupational Safety and Health (NIOSH) or the FFP2 standards that are CE certified (World Health Organization, 2009b). However, our study showed that nearly 24% of the HCWs did not identify the appropriate respirator to be used when dealing with active TB patients and that 18% thought surgical masks were protective. These results are in line with other reports in the literature. A study from Ethiopia found that the majority (67.2%) of HCWs surveyed wrongly believed surgical mask can protect health workers from inhaling *M. tuberculosis* containing droplets (Demissie Gizaw et al., 2015). In Uganda, only 34% of HCWs investigated knew that surgical masks do not protect the wearer from getting TB (Buregyeya et al., 2016) and Kanjee et al. (Kanjee et al., 2011) reported that 11% of HCWs from a hospital in South Africa could not differentiate between a N95 and a surgical mask when presented with one. The proportion was higher in a study from Ethiopia where 68% of HCWs could not identify different types of mask (Demissie Gizaw et al., 2015). Among Russian TB HCWs, 40% knew to wear respirators in units with infectious patients, but many did not know respirators should also be worn where cough-inducing procedures are done or in homes of infectious patients (Woith et al., 2010).

Studies have also reported varying knowledge regarding other TB infection prevention and control measures. HCWs from a hospital in South Africa were found to have high knowledge regarding TB transmission including being generally well informed regarding key routes of TB transmission (Kanjee et al., 2011). A report from healthcare facilities in Ethiopia found that nearly two-third (63.9%) of HCWs had good overall knowledge about TB infection control (Demissie Gizaw et al., 2015). This proportion was lower than that reported in a study conducted in West Gojam which was 74.4% (Temesgen, 2011) and survey results of hospital staff in South Africa (Kanjee et al., 2011). In Uganda, 62% of HCWs were judged to have adequate knowledge of TB infection control, but only 7% answered all related questions correctly (Buregyeya et al., 2016). On the other hand, in Nepal, knowledge on TB infection control was poor among nearly half (45.5%) of HCWs (Shrestha et al., 2017). Only 55% of HCWs could differentiate between TB infection and TB disease. Regarding the infection control measures to be implemented in health facilities, 55% of them stated personal respiratory protection followed by environmental controls (47.4%) and administrative controls (14.7%).

Similarly, poor knowledge regarding infection prevention and control were observed among Russian TB HCWs with only 9% correctly identifying the factors that affect infectiousness of a TB patient (Woith et al., 2010). Moreover, less than 45% knew when personal respirators should be used, what methods can help decrease the presence of the TB organism in the air and only 17% could identify the three types of controls which should be part of a TB program. While some of the difference in results among studies may relate to difference in methodologies and settings, they all identify gaps in knowledge relating to TB infection prevention and control among HCWs. These may be translated to poor practices contributing to TB transmission among patients and HCWs.

4.10.2 Factors associated with knowledge of tuberculosis and its management among healthcare workers

In our study, TB knowledge scores among HCWs differed with respect to a number of factors. Scores differed significantly depending on Age, level of education and occupation. HCWs in the older age groups had a higher knowledge score than those in the younger age groups. Physicians had significantly more knowledge than nurses and other HCWs, while nurses had significantly more knowledge than HCWs other than physicians. In general, HCWs with higher level of education had more knowledge than those with Bachelor or diploma. Knowledge scores also differed significantly depending on the length of work experience. Although not strongly significant, HCWs who deal with TB patients in their non-Hajj work, those who attended a TB seminar in the previous year, and those who were female had slightly higher median knowledge score compared to those who do not deal with TB patients, did not attend TB seminar in previous year or those who were males respectively.

4.10.2.1 Age, gender and tuberculosis training and education

Reports from many countries including Nepal, Uganda, China, India, Iran, Mexico, Mozambique, Ethiopia, Peru, South Africa, Nigeria, and Vietnam did not find significant association between HCWs age or gender and knowledge of TB (Demissie Gizaw et al., 2015, Hoa et al., 2005, Hoffman et al., 2016, Isara and Akpodiete, 2015, Malangu and Adebanjo, 2015, Minnery et al., 2013, Noe et al., 2017).

However, some did find association. For example, Hashim et al. (Hashim et al., 2003), fund significant association between age and TB knowledge among HCWs in Iraq and attributed that to older HCWs having more experience, hence better knowledge. Buregyeya et al (Buregyeya et al., 2016) noted that poor basic TB knowledge was significantly associated with female sex (OR= 0.65; 95% CI: 0.43-1.00). However, in the same study, gender was not a significant factor in relation to specifically knowledge about TB infection prevention and control.

It is reasonable to assume that receiving specific training regarding TB or attending TB seminars, workshops and courses, as well as experience in dealing with TB patients would lead to better knowledge regarding the disease. A number of studies reported such results. Shrestha et al.(Shrestha et al., 2017) found that TB training or orientation received by HCWs in Nepal was significantly associated with knowledge level. These results are in accordance with other reports from Vietnam and Thailand (Hoa et al., 2005, Lertkanokkun et al., 2013). Demissie Gizaw et al. (Demissie Gizaw et al., 2015) found that among HCWs in Addis Ababa in Ethiopia, having been trained in TB infection prevention and control was significantly associated with good knowledge on the subject (OR= 2.41; 95% CI: 1.33-4.36). We found similar association between attending TB seminar in the previous year and level of knowledge of TB among HCWs, although the association was not significant. Yet a study from Nigeria reported that receiving training in MDR-TB was not associated with better knowledge on the topic among HCWs (Isara and Akpodiete, 2015). Similarly, Minnery et al. (Minnery et al., 2013) found that the mean knowledge score among HCWs in Peru was not significantly different in relation to having had training related to TB in the last 12 months or having had TB and/or having lived with someone who had TB.

4.10.2.2 Length of work experience and experience with tuberculosis patients

A study from Mozambique reported the association between experience with TB patients and level of TB knowledge among HCWs. It was found that working with TB patients for one year and between one and 5 years were both associated with increase in knowledge score compared to having never worked with TB patients. Having cared for more than 40 TB patients over the HCWs' career was also associated with increase knowledge compared to those who had cared for less than 10 patients (Noe et al., 2017).

We found similar results in our study, although the association between experience with caring for TB patients and TB knowledge was not significant. In general healthcare work experience has been reported to be associated with better knowledge of TB in some studies but not all. In one study, HCWs with more than 10 years in their job were significantly more knowledgeable about TB than those with less than 10 years' work experience (Hashim et al., 2003).In another study, HCWs who had more than 6-year working experience in health facility were 2 times more likely be knowledgeable about TB compared to those who had less than 3-year experience (OR= 1.97; 95% CI: 1.1-3.5) (Demissie Gizaw et al., 2015). These results are in agreement with our findings and it is argued that more experience and a longer duration of work subject the HCWs to more intensive training courses and evaluation of their promotion by the specialized supervision systems in place under national TB programmes (Hashim et al., 2003). However, a report from Nepal found that duration of employment was not significantly associated with better knowledge among HCWs regarding TB infection prevention and control (Shrestha et al., 2017). Similarly, in South Africa, HCWs with more than 5-years work experience were found not to have better knowledge regarding MDR-TB than those with less than 5-years work experience (Malangu and Adebanjo, 2015).

4.10.2.3 Level of education and occupation

In accordance with results of our study, education level and occupation have consistently been reported to be associated with TB knowledge. A study among HCWs in Southern Mozambique found that greater educational attainment levels were associated with higher TB knowledge scores. Respondents that had attended secondary school and technical college had significantly lower mean knowledge scores than university-educated respondents (Noe et al., 2017). Another report from Ethiopia found that HCWs who had first degree and above were 1.5 times more knowledgeable about TB infection prevention and control compared to those with diploma level (Demissie Gizaw et al., 2015). The above results are in line with data regarding HCWs from Nepal, Ethiopia, Nigeria and Peru and Vietnam (Demissie Gizaw et al., 2015, Hoa et al., 2005, Minnery et al., 2013, Shrestha et al., 2017). Isara and Akpodiete (Isara and Akpodiete, 2015) argued that given the association between education level and knowledge on TB, found in his study, efforts can be made to increase the knowledge of TB in less educated HCWs. In our study, physicians had the highest knowledge scores followed by nurses then other HCWs. In general, clinical staff have been reported to be more knowledgeable about TB than non-clinical staff (Buregyeya et al., 2016).

Physicians in particular were more knowledgeable than nurses and other HCWs and axillary staff such as administrative staff, midwives, laboratory and medical technicians, counsellors and health promoters. In an international study involving HCWs from 4 countries in Asia, South America and the Middle East, being a specialist physician was found to be statistically significant factor associated with health professionals' knowledge scores related to TB treatment (OR= 2.84, 95% CI:1.15–7.05)(Hoffman et al., 2016). In Thailand, Lertkanokkun et al. (Lertkanokkun et al., 2013) reported that various professions had a significantly different level of TB knowledge. Over 70% of physicians had a good level of TB knowledge but only 18.4% of medical technologists / laboratory technicians demonstrated a corresponding level of understanding. Shrestha et al. (Shrestha et al., 2017) also reported significant differences in level of knowledge regarding TB infection prevention and control among different categories of HCWs. They reported that knowledge level was relatively good among medical staff compared to administration staff and was much lower among ward/support staff. They attributed this difference to the fact that medical staff have TB and infection control components covered during their study and are also likely to have received relevant training. Noe and colleagues (Noe et al., 2017) found that among HCWs in Sothern Mozambique, doctors had the highest knowledge scores, and nurses and midwives were the two poorest performing professions in the knowledge section. Similarly, among Russian TB HCWs, physicians had significantly higher TB knowledge scores than nurses, laboratorians, and support staff (Woith et al., 2010). Nurses and laboratorians scored significantly higher than support staff. Minnery et al. (Minnery et al., 2013) found that among front-line TB HCWs in Peru, doctors and nurses had the highest mean TB knowledge scores compared to other HCWs.

Gaps in knowledge regarding TB among HCWs in generals can have important implications not only in increasing the risk of infection among HCWs and patients but it could also lead to inadequate or incomplete information passed on to TB patients. This may create wrong perceptions in them or strengthen the patients' own perceptions, which are often times based on cultural beliefs and misconceptions (Isara and Akpodiete, 2015). This is particularly relevant for first-line staff who are usually at close contact with TB patients and are an important source of information regarding the disease.

The observation that nurses have significantly lower knowledge regarding TB than doctors can have clinical implications as well, as generally doctors develop care plans for patients which nurses then implement. As a result, patient care may be adversely affected if a nurse fails to comprehend the fundamentals behind clinical decisions (Noe et al., 2017).

Lack of knowledge regarding TB among axillary and non-clinical staff is particularly concerning. This is especially true among health promoters and counsellors who are an important group in educating and informing patients regarding TB. Minnery et al. (Minnery et al., 2013) found that among front-line TB HCWs in Peru, doctors and nurses had the highest mean TB knowledge scores compared to nurse technicians, other HCWs and health promoters. The latter group had the lowest level of TB knowledge among HCWs in the study. Another study from South Africa reported that while more nurses and pharmacists had an insufficient level of knowledge regarding MDR-TB as compared with medical doctors, this deficit in knowledge was even more pronounced amongst counsellors, as 71.4% of them were deemed to have insufficient level of knowledge (Malangu and Adebanjo, 2015). The latter findings are similar to reports by other investigators such Kiefer et al. (Kiefer et al., 2009) and Ahmed et al. (Ahmed M. et al., 2009) raising some concerns in that counsellors who educate patients about TB are themselves not so knowledgeable about it. Thus, there have been calls for TB educational needs among HCWs to be determined according to job categories and programs designed to address knowledge gaps according to occupation and educational backgrounds (Woith et al., 2010). This include the need to train non-clinical, auxiliary and support staff (Buregyeya et al., 2016, Shrestha et al., 2017, Woith et al., 2010).

4.10.3 Attitude of healthcare workers toward tuberculosis

Attitude may reflect on how people feel about certain subjects or issues or describes a way of thinking about a situation. Attitude may also refer to the tendency to react in a distinctive way to certain situations, to see and interpret events pertaining to certain tendencies or to assemble opinions into an interrelated structure (Wahab et al., 2016). Our data suggest that HCWs in general had positive attitude regarding TB and TB patients with nearly 85% scoring above average or good attitude score. Most HCWs were willing to be educated on TB and teach others, follow infection prevention measures and trust lab diagnostic results. Also, most would not resign if they were posted to a TB clinic/ward and had no issues examining or treating a TB patient.

Yet, we identified some poor attitudes especially in relation to willingness to work in TB clinic/ward and management and treatment of TB patients. We also found that HCWs were not aware of the actual risk of TB infection related to their work as 30% thought they had very low risk of acquiring TB from their patients but a sizable proportion (69%) were worried about acquiring active TB from work. These results are in line with those reported by Tenna et al. (Tenna et al., 2013) among HCWs from Addis Ababa, Ethiopia, where 20% of HCWs thought they had a very low risk of acquiring TB from patients while 71% worried about acquiring the disease from work. Similarly, a report from Uganda found 63% of HCWs surveyed regarding TB infection control were considered to have a high perceived threat of acquiring LTBI at work (Buregyeya et al., 2016). Multivariable analysis found that not having attended TB infection control training was significantly associated with having a low perceived threat of acquiring LTBI at work, (OR= 0.54; 95% CI 0.36-0.81). Suboptimal knowledge regarding TB, its transmission and treatment, HCWs own experiences, the stigma attached to the disease and worry about TB infection among HCWs may explain why 60% of the HCWs in our study were not willing to work in TB clinic/ward.

In a study among staff in a resource-limited rural South African hospital where nosocomial transmission of MDR- and XDR-TB had been reported resulting in death among staff, 82.1% and 42.9% of HCWs were less willing to work in high-risk areas of the hospital or to continue work as a HCW, respectively (Kanjee et al., 2011). Studies reported that HCWs believe there is a stigma associated with TB. In one study from Mozambique, 70% of HCWs agreed that there was a stigma associated with TB and 48.2% of them believed that this stigma was greater than that which is associated with HIV (Noe et al., 2017). About a third of the HCWs believed that their clinical conduct did not contribute to this stigma, while, conversely, many believed that their actions did stigmatise TB patients, citing their use of PPE as sufficient to perpetuate the stigma. The causes and potential impact of stigma relating to TB vary across countries. In a systematic review of 83 studies from across 35 countries, Chang et al.(Chang and Cataldo, 2014) revealed that there were significant cultural variations with respect to TB and the development of stigma and both variations and similarities in the influence of TB stigma on knowledge, attitudes and responses to TB across countries were identified. Two studies from Ghana found that fear of infection is a major cause of TB stigma and this fear results in TB patients being shunned, avoided and segregated (Dodor and Kelly, 2010, Dodor et al., 2008).

In a study done in the Berea district of Lesotho, almost all HCWs (93%) were found to have positive attitudes towards TB infection prevention (Bhebhe et al., 2014). Most (87.6%) were willing to be tested for HIV if diagnosed with TB and would complete TB treatment (97.7%). Furthermore, over 80% were also willing to improve their eating habits to avoid malnutrition or change their work environment as an approach to TB prevention. In addition. most HCWs served were always ready to be screened for TB if they had suggestive symptoms (95.4%), were willing to teach patients and co-workers about TB prevention (96.1%) and were willing to attend seminars for TB prevention (94.6%). We report very similar results as the proportions of HCWs with similar attitudes in our study were 94.4%, 93.6% and 95.2% respectively. However, other studies reported less positive attitude towards HIV and TB testing among HCWs. For example, Kanjee et al. (Kanjee et al., 2011) found that among HCWs in rural South Africa, 40.4% said they would not have felt comfortable undergoing HIV testing and 28.1% would not seek personal TB diagnosis at the hospital if symptomatic. A number of respondents cited stigma or confidentiality concerns as barriers to staff TB or HIV testing. These results are in line with a review findings that the stigma of HIV prevents HCWs from undertaking prevention activities and accessing care (Nyblade et al., 2009). Efforts to reduce the stigma and improve confidentially have been linked to increased staff testing (Uebel et al., 2004, Uys et al., 2009).

General positive attitudes towards TB found in our study are in line with findings from a number of other studies (Bhebhe et al., 2014, Isara and Akpodiete, 2015, Shrestha et al., 2017). Among HCWs in Nigeria, 72% reported to have positive attitude regarding MDR-TB (Isara and Akpodiete, 2015). Similarly, 73% of HCWs from Nepal had positive attitude towards TB infection control(Shrestha et al., 2017). In the latter study, almost all HCWs (98.4%) agreed that they should wear respirators while caring for TB patients. In our study, 82.2% of HCWs declared that they would use facemasks when dealing with pulmonary TB patients even when it is uncomfortable. However, positive attitudes in relation to TB and TB patients are not always common among HCWs. A study from Thailand found that 56.2% of healthcare providers had positive attitudes towards TB, especially in terms of providing TB services (66.98%) and the use of TB-control systems (60%) (Lertkanokkun et al., 2013). Most providers were proud to take responsibility for TB care and said it was their responsibility to increase treatment success rates. However, a majority (60%) expressed negative attitude towards TB patients.

Studies have shown that providers' attitudes towards patients affect actual treatment success. If patients perceived a stigma or they had a feeling providers were showing a negative attitude towards them, there was a greater tendency to drop out of treatment (Dodor and Afenyadu, 2005, Reyes-Guillen et al., 2008). Therefore, positive HCW's attitude to TB patient is an important factor in improving patient's health-seeking behaviour, compliance with prescribed treatment regimen and treatment outcome (Isara and Akpodiete, 2015). It is also important in preventing the development of drug resistance given that peoples' perceptions of TB and patients' non-adherence to anti-TB treatment were reported to be the most important factors in the emergence of acquired resistance (Yu et al., 2002).

In the univariate analysis, our study did not identify statistically significant differences in attitude scores in relation to various factors. However, attitude scores were lower among HCWs who were male, Saudi, physicians, >50 years old, with a master and <1 year work experience. Also, in the quintile regression analysis, occupation and age were significant at the 50th and 75th quintiles respectively. Attitude score was also lower among those HCWs who do not deal with TB patients during their work compared to those who do. In Peru, HCW's attitude scores were reported to differ among different employment groups (Minnery et al., 2013). A study from Thailand found that age of HCWs was significantly linked to attitude towards TB (Lertkanokkun et al., 2013). More HCWs aged <30 years displayed a positive attitude towards TB than older groups. A report from Uganda found that having not attended a TB infection control training was significantly associated with low self-efficacy and low perceived threat of acquiring TB infection among HCWs (Buregyeya et al., 2016).

4.10.4 Tuberculosis practice among healthcare workers

The WHO defines practice as" how people behave" (World Health Organization, 2008a). It means, the reflection and application of rules and knowledge that lead to actions (Wahab et al., 2016). We report that HCWs in our study had generally good practice in relation to TB and its management. The overall mean practice score was higher than that for knowledge or attitude and over 62% of the HCWs were deemed to have good overall practice scores. Only 1% of HCWs were considered to have poor overall practice scores. While this is encouraging, there were a number of poor practices identified among HCWs.

These are in line with other reports from around the world which found either low overall practice score among HCWs regarding TB and its management or found specific poor practices widespread among HCWs (Hashim et al., 2003, Hoa et al., 2005, Kanjee et al., 2011, Lertkanokkun et al., 2013, Noe et al., 2017, Wahab et al., 2016). For example, Demissie Gizaw et al. (Demissie Gizaw et al., 2015) found that practice among 48.6% of HCWs from healthcare facilities in Addis Ababa, Ethiopia, was not satisfactory. They reported an average practice score of 10.3 points out of 17 (60.7%). Noe et al. (Noe et al., 2017) reported that the practice competency regarding TB care among HCWs in Southern Mozambique was low with the average practice score being 3.2 points out of 9 (35.6%).

As with our results, they identified deficiencies in the initial investigation of TB suspects as well as unfamiliarity with anti-TB drugs and regimes. Only 11% of respondents correctly identified the course of action to take when a patient presents with jaundice after recently commencing TB intensive phase treatment. While the majority of respondents noted that they would monitor the liver enzymes, they failed to relate the occurrence of jaundice to TB treatment (Noe et al., 2017). In our study, the majority of HCWs (90.7%) who the question was applicable to, declared that they request liver function tests before starting anti-TB treatment. Noe et al. (Noe et al., 2017) noted that a possible reason for the low practice scores in their study may have been the fact that the survey was administered among all HCWs regardless of profession or department; as such professionals may have a lack of experience in dealing with common TB scenarios.

Our study also investigated all HCWs regardless of profession, but we aimed to reduce the effect of this factor by using the option “not applicable” for practice questions, so that HCWs could answer only questions that are applicable to them and their practice. Lertkankkun and colleagues (Lertkanokkun et al., 2013) assessed KAP regarding TB care among healthcare providers in 30 governmental hospitals across Thailand. They reported that some healthcare providers, especially physicians, were not following the national TB control guidelines. Similar findings have been reported from other countries including India, Pakistan, Korea, Ethiopia and South Africa (Ahmed M. et al., 2009, Demissie Gizaw et al., 2015, Hong et al., 1995, Kanjee et al., 2011, Malangu and Adebanjo, 2015, Singla et al., 1998, Vandan et al., 2009).

One study in India revealed some practitioners were not even aware of the practice guidelines (Singla et al., 1998), while others reported that certain HCWs misunderstood the TB control guidelines and were not practicing as per the recommendations (Hong et al., 1995). Other studies highlighted that the availability of guidelines was an issue. In a report from Ethiopia, direct observations indicated that TB treatment guidelines were always available only22.7% of the time (Demissie Gizaw et al., 2015). Availability of TB treatment and control guidelines as well as referring to them and understanding them by HCWs are important in the appropriate implementation of these guidelines and in improving knowledge and practice among healthcare providers.

A study from South Africa found that 62% of HCWs surveyed about MDR-TB indicated that they had their own copy of MDR-TB treatment guidelines and 55% stated that they referred to these guidelines (Malangu and Adebanjo, 2015). Interestingly, level of knowledge regarding MDR-TB was significantly higher among those who referred to the MDR-TB management guidelines compared to those who did not.

4.10.4.1 Personal protection measures

In terms of personal protection measures, our study found that the majority (92.1%) of HCWs stated that they usually perform hand hygiene and wear PPE before contact with PTB patient/TB samples and 83.3% usually wear N95 respirator when performing such duties. However, 16.7% stated that they do not use a respirator when dealing with TB patients or TB samples and 12% declared that they do sometimes use wet or soiled N95 respirators. These results in combination with the lack of knowledge among many HCWs regarding TB transmission routes as well as PPE and facemasks' types and purposes found in this study are concerning. However, the results are not uncommon, as many studies reported similar findings related to lack of knowledge regarding PPE and infection prevention guidelines, to poor practices and not following guidelines or to personal comfort and/or unavailability and cost of PPEs in question (Bhebhe et al., 2014, Kanjee et al., 2011, Nettleman et al., 1994). A study from Ethiopia, reported that 50.2% of participants use respirator whenever they are approaching TB suspected patient (Demissie Gizaw et al., 2015).

During data collection, only 21.3% of the respondent had surgical masks for TB patients and 17.9% had N95 mask for HCWs or patient supporters. These results are better than previously reported from the same country where only 12-21% of HCWs reported wearing a mask or respirator when caring for patients with active TB disease (Temesgen, 2011, Tenna et al., 2013). Even lower figures were reported from Nepal where although 48% of the HCWs questioned were exposed to TB patients up to 25% of their working day, 83% of them never used a respirator and only 10% reported using an N95 mask (Shrestha et al., 2017).

Studies from South Africa, a country with high prevalence of TB, provided more insight into HCWs practice with regards to PPE use. Kanjee et al. (Kanjee et al., 2011) found 54.7% of HCWs surveyed in a government district hospital reported that they "always" use a respirator when in a room with a TB case/suspect, while 37.7% claimed that they "often" do so. However, direct observation showed actual compliance was variable, ranging from 24.1-98.5% by department (Kanjee et al., 2011). Many (43.6%) respondents claimed that they "always" check for a tight facial seal when using a respirator, while 19.6% reported that they did not know how to do so. Staff reported that and insufficient supplies, discomfort and appearance were barriers to wider use of respirators. Bhebhe et al. (Bhebhe et al., 2014) found that while HCWs at a hospital in Lesotho practiced hand hygiene (76%) and used respirator masks (71.3%) for personal protection measures, only half (54.4%) made use of the appropriate respirator (N95). The latter represented only 38.8% of the entire sample size. Even more concerning, a study among HCWs in Botsabelo Hospital in Maseru, Lesotho, found that nearly 17% of HCWs questioned reported that they did not use protective masks when they were in contact with MDR-TB patients (Malangu and Adebanjo, 2015). While most medical doctors and nurses (91.7% and 90.2% respectively) reported wearing protective masks; only 57.1% of the counsellors and 22.2% of the pharmacists reported doing so.

Authors argued that these results are particularly important for pharmacists and counsellors who are, routinely, not provided with protective masks and are thus exposed to infection. Protecting such non-clinical and supporting staff means that their family members and all other persons they interact with will also be protected (Malangu and Adebanjo, 2015).

4.10.4.2 Environmental control measures

With regards to environmental control measures, we report that only 48.8% do open windows when possible in TB patient rooms to increase natural ventilation. A study from South Africa reported that 69% of HCWs questioned stated that they open windows for ventilation and sunlight in TB patients' rooms (Bhebhe et al., 2014). However, 27.1% observed controls to avoid air recirculation into other (non-TB) wards. Another study from Ethiopia reported poor environmental control measures among HCWs in a university hospital in the capital Addis Ababa, where only 43% of HCWs opened windows to increase ventilation in crowded wards (Tenna et al., 2013).

However, two other studies from the same country found better practice. Temesgen (Temesgen, 2011) found that 65% of HCWs from 4 hospitals northwest of Addis Ababa stated that they do open windows before they start work to improve the natural ventilation of the rooms (Temesgen, 2011). In addition, 40% said that they use fan (ventilator)to augment the natural ventilation. Demissie Gizaw et al. (Demissie Gizaw et al., 2015) assessed KAP of HCWs from public health facilities in Addis Ababa in relation to TB infection control and found that 94% of HCWs were opening the window whenever TB suspected or confirmed patients were in the room. However, only 53% of the respondents had opened the window at the time of data collection. Discrepancies among reported and observed practices regarding TB and its prevention and control were also highlighted in study among HCWs in a hospital in rural South Africa. Kanjee et al. (Kanjee et al., 2011) found that most respondents (65.5% and 69.1%) reported that doors and windows, respectively, were "always" open in their work area. Direct observation (during winter days) however, showed large interdepartmental differences in natural ventilation, with open windows ranging from 35.3% in the outpatient TB office to 7.6% in male MDR-TB ward to 99.0% in the radiology department.

Environmental infection control measures for TB are dependent on institutional infrastructural design, the use of ventilation and irradiation, which all require capital investment and may differ from healthcare facility to another. These factors may explain some of the differences among studies highlighted above. However, simpler effective methods have been proposed based on adequate ventilation through the opening of windows and in some settings natural ventilation may outperform mechanical ventilation (Escombe et al., 2007).

Hence, educating HCWs on how to maximize natural ventilation by opening windows is an easy, low cost intervention that may reduce patients' and HCWs' exposure to airborne TB. Yet, some of the constraints reported with natural ventilations may limit its application, including patient comfort and weather. Bhebhe et al. (Bhebhe et al., 2014) argued that the relatively low compliance with opening windows for natural ventilation among HCWs found in their study from Lesotho could be partially explained by the harsh weather conditions in the region with temperatures reaching below 0 ^{o}C during winters. They note that this could possibly contribute to some HCWs not opening the windows for ventilation and keeping doors closed. Weather conditions could also explain the low percentage of HCWs opening windows in TB patient rooms in our study. Saudi Arabia has a hot climate and temperatures are high for many months of the year. Hence, this may discourage HCWs from opening windows in patients' rooms.

4.10.4.3 Administrative control and other tuberculosis patients' management measures

In relation to administrative TB control measures and other TB patients' management practices, we found these varied among HCWs in our study. The majority (>89%) of HCWs stated that they always isolate patients with active TB and separate such patients from those with HIV. A study from South Africa reported that 78.3% of HCWs isolate TB patients or use separate TB wards to house them (Bhebhe et al., 2014), but another study from Ethiopia found a low proportion of HCWs reported patients with active TB disease were separated from other patients (18%), including those infected with HIV (10%) (Tenna et al., 2013).

In our study, most (>88%) HCWs request a sputum test, ensuring that the sample is not saliva, for a suspected TB patient and request contact tracing for all confirmed TB cases. However, only around 74%% order HIV tests for patients diagnosed with active TB and 79% start contacts of the active TB cases who are positive for IGRA/TST on INH/RIF prophylaxis. Over 33% of HCWs would commence anti-TB drugs on suspected TB cases before lab confirmation. Bhebhe et al. (Bhebhe et al., 2014) reported that a higher proportion of HCWs from South Africa screen TB patients for HIV (93.8%), probably given the high rate of HIV in the country. However, they found that only 17.8% of HCWs had good knowledge regarding appropriate collection of sputum. Similar to our results, Hashim et al. (Hashim et al., 2003) reported that most (90%) HCWs from Iraq would trace TB patient's contacts, yet only 38% would ask for 3 direct smear tests for suspected TB patients. The latter proportion increased to 99.5% among HCWs deemed to have good knowledge of TB in the study.

Similarly, a study from Ethiopia reported that less than the third of physicians (27%) and 31% of all HCWs, order sputum examination when suspecting TB, which is much lower than that found in our study (Tenna et al., 2013). In general, several studies from around the world reported poor or inadequate administrative measures and TB patients' management and treatment practices among HCWs (Bhebhe et al., 2014, Hashim et al., 2003, Hoffman et al., 2016, Shrestha et al., 2017).

4.10.5 Factors associated with tuberculosis practice among healthcare workers

Level of education was the only variable that showed statistically significant difference in the univariate analysis. However, length of work experience and occupation were significantly associate with practice scores at the 25th and 75th quantiles respectively. In general, HCWs with higher education and longer work experience exhibited better practice scores. No statistically significant difference in practice scores was found in relation to age, gender, nationality, contact with TB patients or attending TB seminar in the previous year. A number of studies found various factors associated with good TB practice among HCWs (Hoa et al., 2005, Lertkanokkun et al., 2013, Noe et al., 2017, Temesgen, 2011). Demissie Gizaw et al. (Demissie Gizaw et al., 2015) reported that independent predictors for having good TB infection control practice among HCWs from healthcare facilities in Addis Ababa, Ethiopia, were TB work experience, TB training and level of education. HCWs who had experience in TB clinic were 2 times more likely to have good practice than those who had no experience (OR= 1.93; 95% CI: 1.12-3.34) and TB-related training had statistical significant association with practice (OR= 1.48; 95% CI: 1.87-2.51). HCWs who had first degree and above had less likely satisfactory practice compared to diploma (OR= 0.64; 95% CI: 0.47-0.88). Similarly, in Vietnam, Hoe and colleagues (Hoa et al., 2005) found that level of medical education, participation in a TB training course and involvement in TB control activities were all significantly associated with TB practice scores among HCWs.

In multiple regression analysis, attending a TB course and higher medical education were significantly associated with increased practice scores of 0.4 point (95% CI: 0.1–0.8) and 0.2 point (95% CI: 0.1–0.3), respectively.

A study from Mozambique found significant association between TB practice scores among HCWs and level of education, occupation and experience with TB patients (Noe et al., 2017). University educated respondents had greater average practice scores when compared to technical college educated respondents (4.71 points vs 2.97 points, $p= 0.009$). Doctors on average scored 2.77 ($p= 0.033$) and 3.50 ($p= 0.015$) points greater than midwives and other HCWs. HCWs who had never worked with TB patients had lower practice scores than those that had been working with patients for less than one year and between one and 5 years (2.31 points, $p< 0.001$ and 1.66 points, $p= 0.004$, respectively). In our study, we found no statistically significant association between practice scores and HCWs' experience with TB patients. A study among HCWs from China, India, Iran and Mexico reported that several factors were associated with HCWs' practices related to TB treatment. These included: training relating to the care of patients with TB since their last degree (OR= 2.63; 95% CI: 1.05–6.60); being based in a hospital (OR= 1.35; 95% CI: 1.18–1.54); trusting somewhat or completely a systematic review of randomized controlled double-blind trials (OR= 1.78; 95% CI: 1.36–2.35); and reading electronic or paper versions of summaries of articles, reports, and reviews from public and not-for-profit health organizations (OR= 1.42; 95% CI: 1.05–1.92) (Hoffman et al., 2016).

4.10.6 Correlation between tuberculosis knowledge, attitude and practice among healthcare workers

We reported a weak but statistically significant positive correlation between knowledge and attitude and between attitude and practice. This suggests that better knowledge about TB among HCWs translated to a better attitude, which in turns was associated with better practice. Yet, the association was weak and there was no significant association between knowledge and practice scores. Reports in the literature support the notion that there is no simple relationship between the level of knowledge, attitude and behaviours regarding TB and its management among HCWs. In a study from Iraq, Hashim et al. (Hashim et al., 2003) concluded that the relatively good TB knowledge found among their HCWs was not reflected in their practices. This despite the finding that HCWs with good knowledge had statistically significantly better attitude and practice than those with poor TB knowledge. Another study from Ethiopia found that TB knowledge among HCWs was not significantly associated with infection control practice (OR= 1.12; 95% CI: 0.85-1.49) (Demissie Gizaw et al., 2015).

However, similar to our results, the study showed significant positive linear correlations between knowledge and practice (r = 0.237, p= 0.001). Temesgen and Demissie (Temesgen, 2011) reported that although HCWs in Northwest Ethiopia were found to have high knowledge regarding TB infection control, the majority did not demonstrate appropriate practice. However, they found that knowledge was a strong predictor for good practice (OR= 10.66; 95% CI: 5.76-19.72). They attributed the discrepancy between HCWs’ knowledge on the one hand and practice on the other to probable shortage or unavailability of infection prevention supplies such as fans and respirators. Engelbrecht et al. (Engelbrecht et al., 2016) investigated factors associated with good TB infection control practices among HCWs in South Africa. They reported that good attitudes and high levels of knowledge were statistically significantly associated with good TB practices after controlling for all other variables. For every unit increase in attitudes, good practices increased 1.090 times (95% CI:1.016–1.169). Respondents with high levels of knowledge (≥80 %) were 4.029 times (95% CI: 1.550-10.469) more likely to have good practices when compared to respondents with poor levels of knowledge (<65 %).

4.10.7 Interventions to improve knowledge, attitude and practice regarding tuberculosis among healthcare workers

4.10.7.1 Education and training

The WHO Global Plan to Stop TB (World Health Organization, 2006a) acknowledges that the main human resource issues affecting TB control are insufficient quality, quantity and distribution of HCWs. According to the Stop TB Partnership, $US 250 million is required annually to provide training and technical support to TB endemic regions. Training of HCWs is an important strategy for improving their productivity and KAP in relation to TB, and the WHO has produced a number of TB training modules for HCWs (World Health Organization, 2006c, 2009a). In such regard, studies from around the world report that health education and training have an impact in improving KAP relating to TB not only among HCWs but also among patients and the community (Bisallah et al., 2018, Hatzenbuehler et al., 2017, Jadgal et al., 2015, Liu et al., 2015, Olayemi et al., 2009). For example, Bisallah et al. (Bisallah et al., 2018) reported that a health education intervention program implemented at a general hospital in Nigeria was effective in improving KAP regarding TB among HIV patients.

The program was delivered through a 6-hour module and a booster session at 3 months using various methods and materials included lectures using PowerPoint slides and posters, discussion sessions and questions and answers to re-enforce learning. The module compromised of an information component and a motivation section. The information component provided information on basic facts about TB, modes of transmission, prevention, risk factors as well as vulnerability and misconception related to the disease. The motivation component was aimed at countering misconceptions about TB leading to positive attitudinal change. Similarly, a brief, one-time, TB educational intervention discussing TB bacteriology, epidemiology, symptoms, and indications for TB testing/treatment, was an effective method to encourage adolescents in the USA to learn about TB and motivate their uptake of TB risk-factor screening, testing and treatment (Hatzenbuehler et al., 2017).

In relation to HCWs, TB training is incorporated into the basic training curriculum of most HCWs including physicians, nurses, community health officers and laboratory technicians in most developed and developing countries. However, the quality of such training varies widely within and between countries (Awofeso et al., 2008, World Health Organization, 2002). The quality and sustainability of integrated TB programs depend critically on the extent to which such basic training is of uniformly high quality (World Health Organization, 2002). Post-basic training for TB control is inadequately funded by most developing countries (Awofeso et al., 2008). Given that HCWs deployed for Hajj come from varied geographic and educational systems backgrounds (in our study, HCWs originated from 17 different countries in North Africa, Middle East and Asia) it becomes important that these HCWs receive tailored, high quality and periodic education on TB and its management as part of their standard work and before deployment to Hajj.

The results of our study indicate the importance of HCWs training and education in relation to all aspects of TB and its management. There is as yet no international consensus regarding the relative emphasis that should be placed on the training of HCWs in order to produce an optimal human resources mix for TB control (Buchan and Dal Poz, 2002). However, relatively small investments focused on HCWs may result in considerable knowledge gains across large populations, hence wider benefits (Laxminarayan et al., 2009). Training is considered to be one of the related factors that influences HCWs regardless of cultural and ethnic background, practice settings, preferred sources of information and learning styles (Wahab et al., 2016).

This is important in the context of HCWs deployed during Hajj as these come from various geographic, ethnic, cultural and institutional backgrounds. A comprehensive approach to TB education and training which includes not only imparting adequate knowledge, but also the much more difficult task of influencing the practices of HCWs, is required. Enhanced teaching and learning methods that deliver information so as to maximise its effect on attitudes and practice patterns are needed. These should not only emphasise the theoretical aspects of training but also skill-based components utilizing adult learning approaches aimed at modifying HCWs' behaviour in order for training to have an impact on practice (Shrestha et al., 2017, Temesgen, 2011). In addition, TB educational needs among HCWs should be determined according to job categories and TB programs designed to address knowledge gaps according to occupation and educational backgrounds (Woith et al., 2010). However, training on the basics of TB and TB infection prevention and control should be provided for all HCWs. Particularly, there is a need to train non-clinical, auxiliary and support staff on TB and TB infection control in order to improve their knowledge, attitudes an practice and prepare them to safely work in high risk settings such as TB care (Buregyeya et al., 2016, Shrestha et al., 2017, Woith et al., 2010). The education of support staff is challenging because of their educational background and special attention may be required to develop appropriate educational programs and materials for this category of workers.

Several means of bringing about behavioural change among health professionals have been reported and may be used to inform the appropriate education and training interventions for HCWs during Hajj. These include traditional and non-traditional methods such as audit and feedback, distribution of education materials, educational meetings, local opinion leaders, outreach visits, reminders, small group discussions and simulated cases, to teach management and role-plays to teach methods of evaluation of case-finding and treatment (Hoa et al., 2005, Hoffman et al., 2016). Rather than single training sessions, some called for multiple behavioural change interventions to be used with ongoing monitoring and evaluation of effectiveness to ensure successful implementation (Kanjee et al., 2011). Promoting distance learning as well as on-site training programs is also important. Distance learning is not necessarily synonymous with Internet-based learning, since other means such as postal correspondence courses and radio and television media may be used to supplement on-site clinical training for improving knowledge and skills for TB control (Awofeso et al., 2008).

Specifically educating and training HCWs in relation to TB infection prevention and control are paramount given that all HCWs are at risk of TB infection and they represent an essential component for the success of TB programs. For instance, simply making HCWs aware of necessary infection control measures like triage, proper sputum handling, respiratory hygiene and patient education can significantly minimise the risk of TB transmission in healthcare settings (Shrestha et al., 2017, Wu et al., 2017a). Some argued that such educations should be delivered as part of a larger effective and sustainable TB infection control program that works within the financial and structural limitations of the healthcare environment and involve the healthcare community in the planning and subsequent implementation of infection control interventions including staff education and training (Tenna et al., 2013).

In the context of Hajj, the Saudi Ministry of Health has a rigorous infection prevention and control training and educational program for HCWs deployed for Hajj, beyond the standard training programs these HCWs undertake throughout the year in their own healthcare facilities across the Kingdom. All HCWs deployed during Hajj are required to complete training to acquire a Basic Infection Control Skills License (BICSL). The latter involve five basic components: proper hand hygiene, proper use of PPE, application of the N95 fit test, principles of safe injection practice as well as compulsory influenza and meningococcal vaccination. The Kingdom also ensures that healthcare centers and hospitals providing services for pilgrims are equipped with the necessary facilities for infection prevention. During the 2017 Hajj, 403 isolation rooms, 168 negative pressure rooms and 461 HEPA filters were available at the Hajj healthcare facilities (General Directorate of Infection Prevention and Control, 2017). The Saudi Ministry of Health also has developed various policies and procedures in relation to infection prevention and control including those specifically for Hajj and it has published various related guidelines, to help HCWs develop their knowledge and skills in the area and adhere to best practices. In addition, various trainings and drills are conducted pre-Hajj for HCWs as per their function and in relation to a number of possible infectious risks. Despite all these efforts, deficiencies in HCWs knowledge and practices in relation to infection prevention and control during Hajj have been documented (Ghabrah et al., 2007) including in our study.

In addition, the above activities are not specifically related to TB but more general overarching infection prevention and control principles or to topical diseases such as the Middle East Respiratory Syndrome (MERS). Specific TB infection prevention and control training may be required for HCWs participating in Hajj or those working in the holy cities serving Umrah pilgrims all-year round.

Educational and training activities alone or in combination with other intervention were reported to have improved HCWs' KAP regarding TB and reduced nosocomial transmission of the disease (Awofeso et al., 2008, Naidoo et al., 2011, Okeyo and Dowse, 2018, Schmidt et al., 2018). Reports by Blumberg et al. (Blumberg et al., 1998, Blumberg et al., 1995) found that expanded staff TB education as well as other TB prevention measures reduced the risk of TB infection among HCWs. Similarly, Jarvis et al. (Jarvis, 1995) reported that education of HCWs for earlier recognition, diagnosis and rapid isolation of TB patients alongside other TB prevention interventions reduced nosocomial transmission. Naidoo and colleagues(Naidoo et al., 2011) reported that a 28-day comprehensive TB training program based on WHO training modules lead to improvement in the overall knowledge of nurses, doctors, and other HCWs. Although the change was not clinically significant, it was statistically significant, with mean total knowledge score increasing from 59.5% pre-training to 66.5% post-training ($p<0.001$). The authors concluded that periodic field training and supervision should be considered to ensure TB knowledge improvement. Experiences in Kyrgyzstan (Awofeso et al., 2008) and the Democratic Republic of Congo (Vanden Driessche et al., 2009) show that periodic training and supervision in the field can improve HCWs' TB knowledge and skills. In Malawi, lay HCWs who underwent a knowledge translation strategy, combining educational outreach and reminders, reported that the intervention was beneficial in increasing their TB, HIV, and job-specific knowledge; improving their clinical skills; and increasing their confidence and satisfaction with their work (Puchalski Ritchie et al., 2016).

Simple and innovative ways of communicating information and training can have great benefits. Okeyo and Dowse (Okeyo and Dowse, 2018) reported that in South Africa, a user-friendly, simple, pictorial-based booklet significantly improved community health workers' knowledge regarding TB (overall knowledge increased from 70.6% to 85.3%, $p<0.001$).

The booklet also contributed to enhanced confidence in their role by facilitating better communication with patients and improving patient trust. They found that key factors influencing the ease of use, and therefore the acceptability, of the booklet was the collaboration with the community health workers during the design process, careful consideration of booklet content and format as well as the inclusion of well-designed pictograms. These findings are in line with reports from the literature highlighting the fact that simply producing written materials for HCWs is not sufficient to improve training and education. There is also a need to improve the usability of written materials such as guidelines to ensure they are clear, easy to use, visually attractive and in the appropriate language. This should be coupled with a better understanding of local needs prior to the design of materials, which can be achieved by ensuring active participation of HCWs (Pakenham-Walsh and Bukachi, 2009). Similar techniques could be used for Hajj as it is the case for some other health-related information, to improve KAP of HCWs in relation to TB especially among non-clinical staff and heath consolers. Such written information, enhanced by visual aids such as pictograms, can enhance comprehension and recall of information and strengthen patient communication by guiding health providers in consistently offering accurate information, which promotes adherence with guidelines and reduces guesswork (Houts et al., 2006, Okeyo and Dowse, 2018).

Finally, training HCWs in research methodologies and understanding and interpreting findings of studies in the area of TB, as well as encouraging them to participate in research, and to read and keep up with relevant recent scientific literature in the field would also be beneficial. This is important given that in our study it was apparent that not all HCWs were up-to-date on new techniques for TB diagnosis and management. Working with researchers, trusting systematic reviews of randomized controlled double-blinded trails, and reading summaries and articles, reports and reviews were all reported to be factors associated with better knowledge and practice relating to TB treatment among HCWs (Hoffman et al., 2016).

A crucial part of any training intervention is its evaluation to determine whether it has been successful, and to inform decisions about future investments (Habicht et al., 1999). Such systematic measurement of intended outcomes of training activities also helps determine whether training objectives were achieved, and whether the accomplishment of those objectives resulted in enhanced performance on the job as well as helping to ensure training meets the needs of learners and organizations (Kraiger et al., 1993, Wu et al., 2017a).

Awofeso et al. (Awofeso et al., 2008) argued that evaluation of the contribution of training to improving HCWs' productivity and the quality of TB control programs should occur at three levels. First, during training, through feedback from participants, quality of written and practical training-related assignments undertaken by participants, and pre-/post-test evaluations. Second, within 1 year following training, through the use of questionnaires to facilitate participants' assessment of the impact of training on their performance, as well as site visits by trainers, to observe participants in clinical and field conditions. Finally, evaluation of TB program outcomes, with particular attention to improvements in case detection rates and cure rates (Awofeso et al., 2008)

Evaluators of the impact of any future Hajj-specific TB training for HCWs should take the above into account as well as being aware of the best approach for evaluation of such training including the limitations of each evaluation strategy (Wu et al., 2017a, 2017b) for instance, pre-and post-training tests, a method that is best suited for testing retention of factual knowledge, does not evaluate improvement in service quality as it does not assess behavioural change among HCWs. Post-training tests conducted immediately after the training sessions do not evaluate long-term knowledge gains. Assessment of behavioural change that is based on qualitative research largely relies on self-reported information and the actual on-the-job performance and practice of trainers is not objectively evaluated.

Wu et al (Wu et al., 2017a) systematically reviewed the literature on the methods and outcome indicators used in evaluating the impact of healthcare provider training to improve TB management. In the 21 eligible studies included in the review, the most common evaluation methods were a review of patient records (38%), post-training interview with trainees (33%) and pre- and post-training tests (28%). In terms of outcomes, more than half of the studies (57%) evaluated knowledge acquisition of trainees, with only (29%) assessing on-the-job behaviour change. The review concluded that publications from robust evaluations assessing the impact on quality of care and behaviour change of TB training among HCWs was limited.

4.10.7.2 Addressing other factors beyond training and education

While appropriate training and education of HCWs are crucial to improving their KAP regarding TB, such activities alone may not be sufficient for improving HCWs performance as well as the quality of TB control outcomes (Awofeso et al., 2008). This is because trained human resources operate in a "productivity mix" involving other factors including personal and lifestyle-related factors, living circumstances, adequacy of preparation for work during pre-service education; health-system related factors such as human resources policy and planning as well as availability of required chemotherapy and supplies for appropriate patient care; job satisfaction-related factors such as financial remuneration and incentives, working conditions, management capacity and styles, professional advancement and safety at work (Dielman and Harmmeijer, 2006). It is important that interventions to improve HCWs KAP address other factors of the 'productivity mix', beyond training, so as not to reinforce the limitations and weaknesses of current practices.

It has been shown that absence of TB management and infection control policies and guidelines, both at national and institutional levels, deficiency in the required protective equipment, shortage or maldistribution of medical personnel as well as structural contains within healthcare facilities can all lead to poor practices among HCWs in relation to TB (Hoffman et al., 2016, Malangu and Adebanjo, 2015, Shrestha et al., 2017). Appropriate funds should be allocated for the purchase of required protective equipment and supplies and clinical practice management guidelines and manuals as well as addressing lack of ventilation and irradiation and structural issues within healthcare facilities to improve TB management and control and reduce the risk of nosocomial transmission (Malangu and Adebanjo, 2015, Tenna et al., 2013). Our study did not investigate the above factors and whether they impacted HCWs knowledge and practice, however, such factors have been identified as possible contributors to poor knowledge and practice among HCWs in relation to TB and its prevention and control (Bhebhe et al., 2014, Demissie Gizaw et al., 2015, Hoffman et al., 2016, Lehmann et al., 2008, Malangu and Adebanjo, 2015, Shrestha et al., 2017, Wajanga et al., 2014). During the Hajj mass gathering, HCWs have to work within the structural limitations of the healthcare facilities they are assigned to as well as within a health system that is performing to near surge capacity for the duration of the pilgrimage.

Although 1000s of HCWs are deployed to work in Hajj health facilities and a huge investment is dedicated each year to supplying and maintaining these facilities for Hajj, the overwhelming number of pilgrims seen at these health facilities during the Hajj may also result in suboptimal practices in relation to TB.

4.11 Study strengths and limitations

The current study investigated KAP related to TB, a disease of national and global concern, including during mass gatherings such as the Hajj (World Health Organization, 2017b, Zumla et al., 2016). The survey instrument used in our study was developed based on existing questionnaires published in the literature and was pilot tested and assessed for both reliability and validity, ensuring a rigorous methodological process. The study enrolled a large number of HCWs of different occupations from numerous healthcare facilities in Hajj. The sample size however represents a small proportion of the 1000s of HCWs deployed to work in Hajj each year. The latter in addition to the cross-sectional design of the study limits the generalizability of the findings as the results may not be representative of all HCWs working cross all Hajj healthcare facilities.

Being a KAP study, it does underestimate the psychological variables that have proved influential in health-related behaviors (Sridhar et al., 2016). Similar with other public surveys, the data collected in our study is based on self-reported information which depends on the honesty and recall ability of the respondents, as well as their understanding of the questionnaire. In such regards, the study collected data using an anonymous self-administered questionnaire, which increased the likelihood of obtaining honest answers from participants. Although it is expected that participants would answer questions honestly, studies that used researches to collect data report that the presence of the researchers might influence HCWs in such a way that they might answer in a manner that they perceived as correct. Presence of researches could also lead to social desire bias as some respondents might give the answers that they thought the researcher was looking for and thus not their true response (Demissie Gizaw et al., 2015). In addition, some argued that even with anonymous surveys, presence of researcher at the time of data collection can also lead respondents to not be truthful about their knowledge, attitudes and practices, fearing that their supervisors would be informed of their responses (Kanjee et al., 2011).

The study did not restrict the participants to a specific occupation and included various HCWs such as physicians, nurses, laboratory staff and other supporting and non-clinical staff. It may be argued that if the study was restricted to only clinical personal, better KAP scores would have been observed. Noe et al. (Noe et al., 2017) stated that the low scores reported in their KAP study regarding TB among HCWs in Southern Mozambique may have been related to the fact that the survey included all HCWs regardless of profession or department. As such, HCWs may have lacked experience in dealing with common TB scenarios affecting their scores. Numerous studies report that clinical staff have better knowledge attitude and practice regarding TB than supporting and non-clinical staff (Buregyeya et al., 2016, Demissie Gizaw et al., 2015, Lertkanokkun et al., 2013, Malangu and Adebanjo, 2015, Minnery et al., 2013, Noe et al., 2017, Shrestha et al., 2017). We have addressed this issue in our study by doing ad-hoc analysis by occupation and also by including the “non-applicable” options in appropriate questions. Moreover, including all HCWs (clinical and non-clinical) in our KAP is considered by some as a strength (Buregyeya et al., 2016, Demissie Gizaw et al., 2015). This is because the resulting data gives a more general picture of the KAP of HCWs who are all, directly or indirectly, part of the management of TB patients and infection prevention in healthcare facilities. In addition, HCWs working at a healthcare institution were found at risk of nosocomial transmission of TB regardless of actual profession, including axillary staff and non-clinical staff (Menzies et al., 2007).

Another limitation of the study is that information on attitude regarding TB was assessed using a questionnaire therefore responses obtained are prone to information bias. A qualitative method such as focus group discussion would be more beneficial to explore beliefs and attitudes relating to TB (Isara and Akpodiete, 2015). Similarly, we did not measure actual practice by observing staff behaviour in a specific situation or by using the simulated client method. The use of self-reported data to assess health professionals’ practices may have predisposed study findings to social desirability bias, which may have caused reported practices to differ from actual behaviour. A review performed by Adams et al. (Adams et al., 1999) suggested that self-reporting of practices might overestimate actual behaviour by up to 27%. Hence, there may have been an overestimation of good practice among HCWs. Studies observing practices would yield more accurate data than using self-administered questionnaires.

On the other hand, measures of actual practice alone will not be able to separate the impact of knowledge and competency, or what is missing on these levels, from other factors (Hoa et al., 2005).

It is also noteworthy that the current study only measured variables that were self-reported by the HCWs and did not take into consideration other factors that may impact practice such as availability of resources required for the implementation of TB infection prevention and control measures. This could have affected the results, as the respondents who reported poor practice may have done so because of non-availability of resources (Bhebhe et al., 2014).

4.12 Summary

In summary, a KAP survey was conducted among 540 HCWs from 13 hospitals serving pilgrims during the 2016 Hajj. In general, we report that HCWs had average knowledge, above average attitude and good practice regarding TB, based on our scoring system and cut-off points. Knowledge gaps were identified in relation to the definition of MDR-/XDR-TB and LTBI, smear microscopy results, length of standard TB treatment for drug-sensitive TB, 2nd-line anti-TB drugs, BCG vaccination, and appropriate PPE to be used with active PTB patients. Poor attitudes were found in relation to willingness to work in TB clinic/ward and to the management and treatment of TB patients. In addition, HCWs were not aware of the actual risk of TB infection connected with their work. Poor practices were reported for commencing anti-TB treatment on suspected TB cases before laboratory confirmation and in increasing natural ventilation in TB patients' rooms. The findings can serve as a baseline to identify key knowledge gaps and poor attitudes and practices in relation to TB and its management among HCWs during Hajj and to design effective interventions to address these shortcomings. Further studies at larger scales including qualitative methods and observation of actual practices as well as considering availability of resources and other possible infrastructure constrains are warranted.

Chapter 5: Summary, strength, limitations and recommendations

5.1 Summary

TB remains a global public health problem with significant morbidity and mortality. In 2017, the WHO estimated that 10 million people developed TB, 9% of whom were infected with HIV. International travel, migration and movement of human populations facilitate the spread of TB.

Undiagnosed and unreported TB are significant issues that contribute to the transmission of TB and challenge TB control efforts worldwide. The WHO estimates that around 36% of people with TB worldwide are either not reported or not diagnosed (World Health Organization, 2015b, 2018b). Under-diagnosis can occur for reasons such as poor geographical and financial access to healthcare, lack of or limited symptoms that delay seeking of healthcare, failure to test for TB when people do present to health facilities, and diagnostic tests that are not sufficiently sensitive or specific to ensure accurate identification of all cases (World Health Organization, 2018b). Numerous studies reported that a sizable proportion of hospitalised patients as well as individuals in the community have undiagnosed active PTB.

International travel, migration and movement of human populations facilitate the spread of TB. In this context KSA is particularly relevant because of its large expatriates' population, mainly from TB-endemic regions, and its yearly hosting of the Hajj and Umrah mass gatherings. Hajj represents many of the risk factors for transmission of respiratory infections including TB. The event is one of the largest mass gatherings in the world characterized by a large elderly population, frequently with underlying health conditions, many of which originate from low income countries where TB is endemic (Al-Orainey, 2013). Pilgrims gather in close contact to perform physically exhausting religious rites, conditions that facilitate TB transmission. In addition, participating in Hajj may also render pilgrims susceptible to reactivation of LTBI (Ai et al., 2016, Al-Orainey, 2013).

With respect to Hajj, as pilgrims are not screened before entry to the Kingdom, it is likely that some may enter Saudi Arabia with active PTB. Because respiratory tract infections and cough are common among pilgrims, patients are often diagnosed with upper respiratory tract infections and only those requiring hospitalisation may be thoroughly investigated (Al-Orainey, 2013). This means that potentially many undiagnosed and untreated active PTB cases are brought to the Kingdom and infection could be transmitted to other pilgrims and to local citizens (Yezli et al., 2017b). Pilgrims infected during the pilgrimage may also spread the infection to contacts in their countries. Transmission of MDR-TB is a real concern as MDR-TB requires long, expensive and extensive treatment with multiple, potentially toxic drugs and outcomes are poor (Orenstein et al., 2009). Also, given the short period pilgrims stay in the Kingdom, short inpatient stay and patients load at healthcare facilities during Hajj, TB cases may be missed among hospitalised pilgrims This may contribute to poor outcome and represent a potential source of TB infection among pilgrims, other patients and HCWs. While both diagnosed and undiagnosed TB has been reported in Hajj among pilgrims, little data is available on the prevalence of active or LTBI during Hajj or the true burden of the disease during the event (Zumla et al., 2016). To address this knowledge gap, the current study aimed to determine the burden of undiagnosed TB among non-hospitalised and hospitalised pilgrims during Hajj.

For non-hospitalised pilgrims, a large-scale screening for active PTB was conducted among pilgrims attending the 2016 Hajj. The 1,510 pilgrims screened originated from 16 countries in Africa, former Soviet countries and South Asia. The study found that 0.66% of pilgrims with cough from medium/high TB burden countries (mostly from India and Afghanistan) had active PTB. TB prevalence was higher among males, the elderly, those with low level education, those residing in South Asia, those with underlying health conditions, those with previous TB treatment, those coughing for more than a week, those who have contacts diagnosed or treated for TB, those who lived recently in a household with an adult with cough and those who traveled outside their current country of residency in the previous year. However, the difference was not statistically significant with the exception for underlying health conditions and cough duration. Underlying health conditions and cough in the household were independent risk factors for TB after adjusting for other variables. Pilgrims with underlying health conditions were nearly 6 times more likely to develop TB (aOR= 5.89; 95% CI= 1.25-27.80). Similarly, those who recently lived in a household with an adult with cough were 4.5 times more likely to have TB (aOR= 4.46; 95% CI= 1.01-19.58).

For hospitalised pilgrims, the study conducted the first screening for active PTB among this population during the 2016 and 2017 Hajj seasons. The 347 inpatient pilgrims screened originated from 44 countries in Africa, Asia, Europe and the USA. Most (over 60%) of patients had an initial and/or final diagnosis of diseases of the respiratory system, particularly pneumonia. The study found that 2.9% of inpatients with cough (mostly from Indonesia and India) had active PTB and most (77.7%) of these were missed by the hospitals including MDR-TB cases. TB prevalence was higher among those with no formal education, those residing in Asia, those with underlying health conditions, smokers, those with previous TB treatment, those coughing up blood, those coughing for more than a week and those admitted to an isolation ward. However, the difference was statistically significant only for previous TB treatment and admission ward. Previous TB treatment was independent risk factor for TB after adjusting for other variables.

Hence, we conducted the first screening for active pulmonary TB (PTB) among hospitalised pilgrims attending the 2016 and 2017 Hajj seasons to determine the burden of TB among this population. We found that 2.9% of inpatients with cough (mostly from Indonesia and India) had active PTB and most (77.7%) of these were missed by the hospitals including MDR-TB cases. TB prevalence was higher among those with no formal education, those residing in Asia, those with underlying health conditions, smokers, those with previous TB treatment, those coughing up blood, those coughing for more than a week and those admitted to an isolation ward. However, the difference was statistically significant only for previous TB treatment and admission ward. Previous TB treatment was independent risk factor for TB after adjusting for other variables. Patient who had history of TB treatment were 8 times more likely to be TB positive after adjusting for other factors (aOR= 8.1; 95% CI= 1.351-48.464, p= 0.022).

In light of the above 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.

Appropriate management of TB cases during mass gatherings such as the Hajj is crucial for better patient outcome and prevention of transmission. Although there are national and international TB guidelines on the management of TB, currently there are no specific guidelines on the management of the disease at mass gatherings. In general, early detection through systematic screening of TB suspects is a major strategy for improving TB case detection. The WHO recommends that persons with signs and symptoms consistent with TB should be evaluated for TB to ensure prompt diagnosis and treatment (World Health Organization, 2011a, 2017a). Similarly, the Saudi TB guideline recommends that HCWs should be knowledgeable about TB symptoms to facilitate the efficient identification of TB suspects for diagnosis and treatment (Saudi Ministry of Health, 2014). The safe and efficient diagnosis of TB disease is also important and depend on the existence of an integrated network of multi-level laboratories with adequate biosafety standards, quality-assured capacity, mechanism for specimen referral and complimentary TB and HIV testing capability (World Health Organization, 2017a). Various diagnostic techniques are available and used including smear microscopy for AFB, culture and modern molecular methods such as the Xpert MTB/RIF and Xpert Ultra assays (World Health Organization, 2017e).

Starting TB treatment early and ensuring people with TB stay on treatment for the entire duration of treatment is a global TB control strategy. TB is curable, but inappropriate regimen prescription and non-adherence to recommended dosages contribute to poor treatment outcomes. The WHO and KSA guidelines both recommend the administration of standardized first-line anti-TB treatment regimen, consisting of an initial 2 months of treatment with INH, RIF, PZA and EMB and subsequently treatment with INH-RIF for the next 4 months. The 6 months TB treatment regimen is recommended for TB patients with drug-susceptible TB, those without prior history of starting treatment with anti-TB agents and those without recognized risk factors for drug resistance, while awaiting DST results (Saudi Ministry of Health, 2014, World Health Organization, 2017a, 2017c). Treatment of RR-TB or MDR-TB is longer and involve more agents (Falzon et al., 2017).

Both the KSA and WHO TB guidelines consider the pursuit of a patient-centered approach to TB treatment, a necessary strategy for promoting treatment adherence, improving the quality of life of TB patients and alleviating suffering (Saudi Ministry of Health, 2014, World Health Organization, 2017a). Treatment monitoring as well as supportive TB management approaches including IPC measures are also crucial for better outcome and prevention of development of drug-resistance and as well as transmission of the diseases.

The TB management approaches during Hajj remained largely undocumented, and it is unknown whether these are consistent with the KSA and international TB management guidelines. The current study documented the management of TB patients during the 2016 and 2017 Hajj seasons and explored the compliance of healthcare providers with the KSA TB management guidelines in the Saudi MOH hospitals during the mass gathering.

The study was conducted over a one-month period (1-30thDulHija, Hajj lunar month) in hospitals in Makkah and holy sites including temporary hospitals operational only during Hajj days. There were 31 cases of drug-susceptible TB and 1 case of extensively drug-resistant TB (XDR-TB). Although the TB patients were nationals of 10 countries, 66.7% of them were KSA residents. Out of a maximum score of 10 for the selected TB management themes, the guideline compliance score was highest for IPC and surveillance (9.6) and identifying TB suspects (7.2). The least scores were obtained for treating TB (5.0) and diagnosing TB (3.0).

About half of the TB patients were separated from other patients at registration in the hospitals. The proportion of TB patients that were isolated in designated isolation rooms/wards rose from 77.4% pre-diagnosis to 96.7% on confirmation of TB diagnosis. All suspected TB patients were correctly screened using appropriate TB symptoms and chest X-ray was conducted for 67.7% of TB patients. Contrary to guideline recommendations, culture was the only diagnostic test applied in nearly 2/3rd of the TB patients. Smear microscopy was done sparingly and no Xpert MTB/RIF assay was conducted for the TB patients. Additionally, only a fraction of TB patients were questioned about their HIV status (20.7%) or tested for HIV (12.9%).

Regarding treatment of drug-susceptible TB, only 37% of TB patients received four 1st-line anti-TB drugs, the majority received either three 1st-line anti-TB drugs (40.7%) or two 1st-line anti-TB drugs (11.1%). For TB notification, all confirmed TB cases with known notification status were reported to the KSA MOH, but the confirmed-TB status of two international pilgrims was not reported to their country health representatives/medical missions.

TB is a global health issue with significant morbidity and mortality.(World Health Organization, 2017b) The WHO's The End TB Strategy has a vision of a world free of TB with the following milestones to be achieved by 2035: 95% reduction in TB deaths compared with 2015, 90% reduction in TB incidence rate, and no affected families facing catastrophic costs due to TB (World Health Organization, 2014b). The early diagnosis and appropriate management of TB cases by a knowledgeable and skilled healthcare workforce are integral for the success of the strategy. HCWs are key component of the success of any TB program, yet they are also at increased risk of TB infection and disease. TB has long been an occupational risk for HCWs although consensus on the matter is relatively recent (Sepkowitz, 1994). High level of knowledge, good attitude and correct practice among HCWs in relation to TB are important factors in the appropriate management of TB cases and reducing the risk of transmission of the disease including in the healthcare setting and to HCWs themselves.

Knowledge deficit regarding TB among HCWs may result in substandard care, ineffective service provision, inefficient resource use, and further inequities in health outcomes as well as risk of TB transmission and development of resistance. Indeed, one of the greatest contributors to MDR-TB is improper treatment that may be prescribed or administered by health professionals, either because of inaccurate diagnosis, insufficient treatment supplies, or limits in their knowledge of evidence-based TB control practices (Langendam et al., 2012, Marahatta, 2010). In addition, the knowledge and attitude of HCWs towards TB will determine the type and quality of information passed on to the patients during health education. Inadequate or incomplete information passed on to the patients create wrong perceptions in them or strengthen the patients' negative perceptions which are often times based on cultural beliefs and misconceptions (Isara and Akpodiete, 2015).

These negative perceptions are mostly inimical to appropriate health seeking behaviour, hence reducing the likelihood of completing treatment and achieving cure and increasing the risk of spread of the disease (Matebesi and Timmerman). As such, the knowledge, attitude and practices of health professionals related to TB affect not only themselves and their individual patients, but also the global population as a whole.

The Hajj religious mass gathering in KSA attracts over 2 million pilgrims from over 180 different countries (Yezli et al., 2017a). Many pilgrims come from TB endemic areas and have risk factors for TB. The event has been linked in increased risk of TB infection and both diagnosed and undiagnosed TB have been reported at the pilgrimage (Alzeer et al., 1998, Wilder-Smith et al., 2005, Yezli et al., 2017b). During Hajj 1000s of HCWs are deployed from across the Kingdom to ensure healthcare for pilgrims. These HCWs receive various specific training before deployment including in infection prevention and control. However, this work force includes HCWs from varying occupations, having different educational levels and work experience and originating from numerous countries. Knowledge gaps as well as poor attitudes and practices in relation to infection prevention and control have been documented among HCWs working in Hajj (Ghabrah et al., 2007). No study investigated KAP of HCWs deployed in Hajj in relation to TB and its management. The current study investigated the latter with the aim of identifying knowledge gaps regarding TB and its management and attitudes and behaviours among HCWs that could facilitate TB transmission or impact on TB management during the event. Hence, exploring potential interventions for improvement.

We conducted a KAP survey among 540 HCWs from 13 hospitals serving pilgrims during the 2016 Hajj. HCWs originated from 17 different countries and included physicians, nurses as well as other HCWs. Nearly half of the participants declared dealing with TB patients during their day-to-day work. In general, we report that HCWs had average knowledge (mean knowledge score of 52%), above average attitude (mean attitude score of 73%) and good practice (mean practice score of 81%) regarding TB, based on our scoring system and cut-off points. Most HCWs (78%) had average or above knowledge score (mean knowledge score >40%) and 84.7% and 90.2% had above average or higher attitude and practice scores respectively (mean attitude or practice scores >60%).

Overall, HCWs were knowledgeable about the cause, main symptoms and mode of transmission of TB, diagnostic and screening tests for TB and LTBI, 1^{st}-line anti-TB treatment, HIV patients' vulnerability to contracting TB and the importance of PPE when dealing with active TB patients. However, knowledge gaps were identified in all the knowledge themes explored in our study. These include the disease's microbiology and epidemiology (especially questions related to the definition of MDR-/XDR-TB and LTBI), TB diagnosis (especially questions relating to smear microscopy results), TB treatment (especially questions relating to the length of standard TB treatment for drug-sensitive TB and 2^{nd}-line anti-TB drugs) and TB prevention (especially questions relating to LTBI, BCG vaccination, and appropriate PPE to be used with active PTB patients).

In relation to HCWs' attitude to TB and TB patients, it was in general positive. Most HCWs were willing to be educated on TB and teach others, follow infection prevention measures and trust lab diagnostic results. Also, most would not resign if they were posted to a TB clinic/ward and had no issues examining or treating a TB patient. Yet, we identified some poor attitudes especially in relation to willingness to work in TB clinic/ward and to the management and treatment of TB patients. In addition, HCWs were not aware of the actual risk of TB infection connected with their work.

Most HCWs reported good practice regarding TB management and infection prevention. Most reported following administrative and personal protection measures such as performing hand hygiene and using PPE when dealing with PTB patients or handling TB samples as well as isolating TB cases from other patients and separating them from those with HIV. Also, good practice was reported in relation to the appropriate measures for contacts of confirmed TB patient and those for suspected TB cases. Poor practice was reported for commencing anti-TB treatment on suspected TB cases before laboratory confirmation and not opening the windows in patient rooms to increase natural ventilation. The latter was probably in part related to the hot weather conditions in KSA, which may discourage HCWs from the practice.

There was a statistically significant difference in knowledge scores in relation to age, gender, nationality, level of education, occupation and length of work experience as well as a significant difference in practice scores in relation to the level of education. Attitude scores did not significantly differ with respect to individual covariates. The significance of the association of the variables with the KAP scores differed across the various KAP score quantiles.

In general, HCWs in the older age groups had better knowledge than other HCWs but there was no difference in attitude or practice among the age groups. Females and non-Saudi HCWs had better knowledge and attitude but worse practice compared to males and Saudi HCWs respectively. Physicians had better knowledge than nurses and "other" HCWs, but this was not apparent for attitude or practice, where "other" HCWs scored better practice than both physicians and nurses. HCWs with longer work experience seem to have better knowledge, attitude and practice than those with shorter work experience. Similarly, HCWs who attended TB seminar/lecture in the previous year seem to have better knowledge, practice and marginally better attitude than those who did not. HCWs with higher level of education had better knowledge and practice than those with lower level of education, but not better attitude. HCWs who had experience with TB patients had better knowledge and attitude than those who did not, but lower practice scores.

There was a weak but statistically significant positive correlation between knowledge and attitude and between attitude and practice. This suggests that better knowledge about TB among HCWs translated to a better attitude, which in turns was associated with better practice. Yet, the association was weak and there was no significant association between knowledge and practice scores.

5.2 Study strength and limitations

The current study has some strength and limitations:

- The investigation into undiagnosed TB among non-hospitalised pilgrims is only the second study to report on this important issue, with a larger sample size from more countries. However, in the non-hospitalised pilgrims' cohort we only screened 1,512 pilgrims from 16 countries which represent only a small proportion of the Hajj pilgrims' populations which exceeds 2 million and originates from over 180 different countries.

Also, the study detected a small number of TB cases among the population investigated. However, As many reports suggest that a sizable proportion of people with TB do not present with cough, the results may be an undestimation of the true prevalence of TB among non-hospitalised Hajj pilgrims. Future studies investigating a larger number of pilgrims from a greater number of countries with large pilgrims' populations and high TB and MDR-TB burdens such as Turkey, Egypt, China, Kenya, Myanmar, Russian Federation, Tanzania and Zambia, are warranted. Finally, while remote, we cannot eliminate the possibility that some of the non-hospitalised pilgrims investigated were already TB patients but chose not to disclose this information to the study investigators.

- The investigation into missed TB among hospitalised pilgrims in Hajj is the first study to report on this significant issue. However, for the hospitalised pilgrims' cohort, the study only screened 304 inpatients symptomatic for cough. While the study systematically enrolled eligible patients, this number represents a small proportion of the total Hajj pilgrims admitted to healthcare facilities each year. Also, the study detected a small number of TB cases among the population investigated. Similar as above, numerous studies have reported TB cases among patients who were asymptomatic or did not have cough. Hence the reported prevalence of TB in the study may be an underestimation of the true prevalence of undiagnosed TB among hospitalised pilgrims in Hajj. On the other hand, the study population is not representative of the broader hospital's population. Future studies investigating a larger number of patients may be warranted.

- For both hospitalised and non-hospitalised pilgrims cohorts, due to 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.(Marais et al., 2013)

- In relation to TB management, the current study is among the foremost surveys of TB management at international mass gatherings. However, the study investigated only a small number of cases and there was a high proportion of unknown responses for some variables. Nevertheless, the TB management indices obtained was a fair representation of the compliance of providers with national and international TB guidelines in MOH hospitals during the Hajj.

- In relation to the KAP of HCWs regarding TB, the current study is the first to investigated this issue Saudi Arabia in relation to a disease of national and global concern, including during mass gatherings such as the Hajj.(World Health Organization, 2017b, Zumla et al., 2016) The survey instrument used in our study was developed based on existing questionnaires published in the literature and was pilot tested and assessed for both reliability and validity, ensuring a rigorous methodological process. The study enrolled a large number of HCWs of different occupations from numerous healthcare facilities in Hajj. The sample size however represents a small proportion of the 1000s of HCWs deployed to work in Hajj each year. The latter in addition to the cross-sectional design of the study limits the generalizability of the findings as the results may not be representative of all HCWs working cross all Hajj healthcare facilities.

- Being a KAP study, it does underestimate the psychological variables that have proved influential in health-related behaviors.(Sridhar et al., 2016) Similar with other public surveys, the data collected in our study is based on self-reported information which depends on the honesty and recall ability of the respondents, as well as their understanding of the questionnaire. In such regards, the study collected data using an anonymous self-administered questionnaire, which increased the likelihood of obtaining honest answers from participants. Although it is expected that participants would answer questions honestly, studies that used researches to collect data report that the presence of the researchers might influence HCWs in such a way that they might answer in a manner that they perceived as correct. Presence of researches could also lead to social desire bias as some respondents might give the answers that they thought the researcher was looking for and thus not their true response (Demissie Gizaw et al., 2015). In addition, some argued that even with anonymous surveys, presence of researcher at the time of data collection can also lead respondents to not be truthful about their knowledge, attitudes and practices, fearing that their supervisors would be informed of their responses (Kanjee et al., 2011).

- The KAP study did not restrict the participants to a specific occupation and included various HCWs such as physicians, nurses, laboratory staff and other supporting and non-clinical staff. It may be argued that if the study was restricted to only clinical personal, better KAP scores would have been observed. Noe et al. (Noe et al., 2017) stated that the low scores reported in their KAP study regarding TB among HCWs in Southern Mozambique may have been related to the fact that the survey included all HCWs regardless of profession or department. As such, HCWs may have lacked experience in dealing with common TB scenarios affecting their scores. Numerous studies report that clinical staff have better knowledge attitude and practice regarding TB than supporting and non-clinical staff (Buregyeya et al., 2016, Demissie Gizaw et al., 2015, Lertkanokkun et al., 2013, Malangu and Adebanjo, 2015, Minnery et al., 2013, Noe et al., 2017, Shrestha et al., 2017). We have addressed this issue in our study by doing ad-hoc analysis by occupation and also by including the "non-applicable" options in appropriate questions.
  Moreover, including all HCWs (clinical and non-clinical) in our KAP is considered by some as a strength (Buregyeya et al., 2016, Demissie Gizaw et al., 2015). This is because the resulting data gives a more general picture of the KAP of HCWs who are all, directly or indirectly, part of the management of TB patients and infection prevention in healthcare facilities. In addition, HCWs working at a healthcare institution were found at risk of nosocomial transmission of TB regardless of actual profession, including ancillary staff and non-clinical staff (Menzies et al., 2007).

- Another limitation of the KAP study is that information on attitude regarding TB was assessed using a questionnaire therefore responses obtained are prone to information bias. A qualitative method such as focus group discussion would be more beneficial to explore beliefs and attitudes relating to TB (Isara and Akpodiete, 2015). Similarly, we did not measure actual practice by observing staff behaviour in a specific situation or by using the simulated client method. The use of self-reported data to assess health professionals' practices may have predisposed study findings to social desirability bias, which may have caused reported practices to differ from actual behaviour. A review performed by Adams et al. (Adams et al., 1999) suggested that self-reporting of practices might overestimate actual behaviour by up to 27%. Hence, there may have been an overestimation of good practice among HCWs. Studies observing practices would yield more accurate data than using self-administered questionnaires.

On the other hand, measures of actual practice alone will not be able to separate the impact of knowledge and competency, or what is missing on these levels, from other factors (Hoa et al., 2005). It is also noteworthy that the current study only measured variables that were self-reported by the HCWs and did not take into consideration other factors that may impact practice such as availability of resources required for the implementation of TB infection prevention and control measures. This could have affected the results, as the respondents who reported poor practice may have done so because of non-availability of resources (Bhebhe et al., 2014).

5.3 Recommendations

The results of the different arms of the current study identified a number of key issues in relation to TB and its management during the Hajj mass gathering (Figure 30). These issues require immediate attention from the Hajj stakeholders including the Saudi MoH, Hajj medical missions as well as the national and international health organizations and regulators such as WHO, the Saudi CDC and international community at large. A number of recommendations can be drawn from the results of the current study as follows:

For the undiagnosed TB among hospitalised and non-hospitalised pilgrims: Given the results of the current study and the potential impact of undiagnosed TB among inpatients and non-hospitalised pilgrims during Hajj, the following recommendations are proposed:

1. Further studies are needed to define the burden and risk of TB as well as its management during Hajj.
2. Further communication and collaboration with the WHO and other stakeholders regarding the outcome of this study and the way forward.
3. Formulate appropriate policies and interventions to prevent infection and transmission of PTB during the Hajj mass gatherings. These may include:
    a. Increase education and awareness regarding TB and its prevention among pilgrims through targeted campaigns to encourage health-seeking behaviour in case of symptoms and adherence to treatment and to general infection prevention measures.
    b. Increase education and awareness regarding TB and its prevention among workers including healthcare workers deployed during the Hajj/Umrah.

c. Explore the idea of 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 to rapidly render them non-infectious.
d. Revise/develop TB-management policies including screening criteria and techniques to best fit the unique Hajj/Umrah conditions.
e. Deployment and the use of rapid, sensitive and specific point-of-care molecular techniques for TB/MDR-TB screening and diagnosis such as the Xpert MTB/RIF and Xpert Ultra assays.

For the TB management study in Hajj: The study results showed high level of compliance with the assessed indices for systematic screening of TB suspects, IPC and case notification, but low compliance scores were obtained for prompt TB diagnosis and use of standardized treatment regimen for drug susceptible TB. Based on observations from the current study a number of recommendations can be proposed. These are as follows:

1. Develop and disseminate an international Hajj and Umrah-specific TB control and management protocol to provide guidance on: TB surveillance, IPC, screening and diagnostic methods, choice of treatment and care models and patient transfer, including strategies for maintaining the continuum of care during and after the mass gatherings.
2. Update the current KSA TB national guidelines to adopt new diagnostic recommendations and to highlight the treatment pathway for drug-resistant TB, in line with current global standards.
3. Improve knowledge and practice of healthcare providers regarding TB management through the provision of training and periodic refresher courses as well as guidance materials.
4. Monitor the TB management practices in MOH and non-MOH health facilities regularly to make recommendations for improvement.
5. Provide the Xpert MTB/RIF Ultra assay testing capability at the point of care to facilitate same day TB diagnosis including MDR-TB.
6. Raise awareness among healthcare providers about the need for mandatory screening and testing for HIV and other comorbidities in suspected TB patients.
7. Consider conducting systematic/targeted TB screening for pilgrims arriving from within the Kingdom for the Hajj, based on a pre-established criteria.

8. Provide at least the full initial 2 months TB regimen to the pilgrims during Hajj and direct them to report and follow with healthcare facilities for the follow up 4 months treatment whether they are in KSA or in their country of residency

For the HCWs KAP study; Given the context of Hajj, the potential global health consequences of mismanagement of TB cases at the event and the results of the current study, and number of recommendations can be made to improve HCWs KAP regarding TB, improve TB management during the event and reduce the risk of local and international TB transmission. These are as follows:

1. Develop tailored, high quality and periodic education and training programmes on all aspects of TB and its management for all HCWs according to job categories and educational backgrounds.
2. Develop training programmes for non-clinical, auxiliary and support staff on TB and TB infection prevention and control in order to improve their KAP and prepare them to safely work in high risk settings such as TB care.
3. A comprehensive approach to TB education and training, which includes not only imparting adequate knowledge, but also the much more difficult task of influencing the practices of HCWs, is required. Such training should not only emphasise the theoretical aspects of training but also skill-based components utilizing adult learning approaches aimed at modifying HCWs' behaviour in order for training to have an impact on practice.
4. Training and education should utilize various means shown affective in bringing about behavioural change among HCWs including traditional and non-traditional methods such as audit and feedback, distribution of education materials, educational meetings, local opinion leaders, outreach visits, reminders, small group discussions and simulated cases, to teach management and role-plays to teach methods of evaluation of case-finding and treatment. Distance learning in the area should also be promoted.

5. Training and education on TB among HCWs should be a continuous process with multiple behavioural change interventions to be used with ongoing monitoring and evaluation of effectiveness to ensure successful implementation. The methods to be used for evaluation have to be appropriate for an objective assessment of the impact of the training interventions not only on knowledge but also on attitudes and behaviours as well.
6. Infection prevention and control training specific for TB may be required for HCWs participating in Hajj. This training could be incorporated as part of the general infection prevention and control preparative measures taken by the Saudi Ministry of Heath Pre-Hajj deployment or could be conducted separately.
7. Special attention should also be given to addressing factors beyond training that could influence HCWs' KAP regarding TB, so as not to reinforce the limitations and weaknesses of current practices. Appropriate funds and resources should be allocated to address lifestyle, health system, job satisfaction as well as Hajj-related factors that could undermine appropriate TB management and control in healthcare facilities during the mass gathering.

Figure 30. Study findings (by the author)

Contributing factors

- HCWs poor KAP in relation to TB
- Short hospitalization
- Eagerness to fulfill Hajj rites
- Pilgrims' lack of knowledge about TB and its prevention
- Pressured health system during Hajj
- International travel and crowding
- Many pilgrims from endemic TB areas
- Inadequacy of TB prevention and management guidelines in the context of Hajj

TB miss-management

Unsuspected TB
- Lack of symptoms
- Unrecognized/missed symptoms
- Inadequate/lack of screening
- Symptoms masked by other comorbidities

TB diagnosis issues
- Lack of appropriate diagnostic tools
- Use of inappropriate diagnostic tools
- Limitations of diagnostic tools

Inappropriate TB treatment
- Inappropriate regiment (agents/duration)
- Failure to adhere to regiment

Failures in TB IPC
- Failure to isolate
- Unavailability/misuse of PPE
- Inadequate IPC practices
- Infrastructure/weather-related issues

Follow up and notification
- Lack of post-Hajj follow up
- Variable heath system capabilities in countries of origin

Consequences

- **Undiagnosed/missed active TB**
- **TB transmission (local and global)**
- **Poor TB case outcome**
- **Development of MDR-TB**

- Develop and disseminate Hajj/mass gathering specific TB control and management guidelines
- Conduct further studies on TB during Hajj for evidence-based policies.
- Monitor TB management practice and health facilities and make recommendations for improvement.
- Increase education/awareness regarding TB and its prevention among pilgrims and Hajj workers.
- HCWs should receive tailored, high quality and periodic education and training on TB including before deployment to Hajj.
- Use in Hajj of point-of care rapid molecular TB diagnostic techniques.
- International engagement to develop optimum strategies to screen for, manage and prevent TB at Hajj.

References

Abbas MA, AlHamdan NA, Fiala LA, AlEnezy AK, AlQahtani MS. Prevalence of latent TB among health care workers in four major tertiary care hospitals in Riyadh, Saudi Arabia. J Egypt Public Health Assoc 2010;85(1-2):61-71.

Abdelmoety DA, El-Bakri NK, Almowalld WO, Turkistani ZA, Bugis BH, Baseif EA, et al. Characteristics of Heat Illness during Hajj: A Cross-Sectional Study. Biomed Res Int 2018;2018:5629474.

Abebe G, Deribew A, Apers L, Woldemichael K, Shiffa J, Tesfaye M, et al. Knowledge, health seeking behavior and perceived stigma towards tuberculosis among tuberculosis suspects in a rural community in southwest Ethiopia. PLoS One 2010;5(10):e13339.

Abouzeid MS, Al RF, Memish ZA. Mortality among tuberculosis patients in Saudi Arabia (2001-2010). Ann Saudi Med 2013;33(3):247-52.

Abouzeid MS, Zumla AI, Felemban S, Alotaibi B, O'Grady J, Memish ZA. Tuberculosis trends in Saudis and non-Saudis in the Kingdom of Saudi Arabia--a 10 year retrospective study (2000-2009). PLoS One 2012;7(6):e39478.

Abruzzi WA, Jr., Hummel RJ. Tuberculosis: incidence among American medical students, prevention and control and the use of BCG. N Engl J Med 1953;248(17):722-9.

Adal KA, Hospital UoV. Preventing Nosocomial Tuberculosis with HEPA Respirators: A Cost-effectiveness Analysis: University of Virginia, 1994.

Adams AS, Soumerai SB, Lomas J, Ross-Degnan D. Evidence of self-report bias in assessing adherence to guidelines. Int J Qual Health Care 1999;11(3):187-92.

Adams S, Ehrlich R, Baatjies R, van Zyl-Smit RN, Said-Hartley Q, Dawson R, et al. Incidence of occupational latent tuberculosis infection in South African healthcare workers. Eur Respir J 2015;45(5):1364-73.

Ahmad RA, Mahendradhata Y, Utarini A, de Vlas SJ. Diagnostic delay amongst tuberculosis patients in Jogjakarta Province, Indonesia is related to the quality of services in DOTS facilities. Trop Med Int Health 2011;16(4):412-23.

Ahmed M, Fatmi Z, Ali S, Ahmed J, Ara N. Knowledge, attitude and practice of private practitioners regarding TB-DOTS in a rural district of Sindh, Pakistan. J Ayub Med Coll Abbottabad 2009;21(1):28-31.

Ahmed QA, Arabi YM, Memish ZA. Health risks at the Hajj. Lancet 2006;367(9515):1008-15.

Ahmed QA, Barbeschi M, Memish ZA. The quest for public health security at Hajj: the WHO guidelines on communicable disease alert and response during mass gatherings. Travel Med Infect Dis 2009;7(4):226-30.

Ahn YS, Lim HS. Occupational infectious diseases among Korean health care workers compensated with Industrial Accident Compensation Insurance from 1998 to 2004. Ind Health 2008;46(5):448-54.

Ai JW, Ruan QL, Liu QH, Zhang WH. Updates on the risk factors for latent tuberculosis reactivation and their managements. Emerg Microbes Infect 2016;5:e10.

Akçakir Y. Correlates of treatment outcomes of multidrug-resistant tuberculosis (MDR-TB): a systematic review and meta-analysis. McGill University; 2009.

Al-Ghamdi SM, Akbar HO, Qari YA, Fathaldin OA, Al-Rashed RS. Pattern of admission to hospitals during muslim pilgrimage (Hajj). Saudi Med J 2003;24(10):1073-6.

REFERENCES

Al-Hajoj S, Varghese B, Shoukri MM, Al-Omari R, Al-Herbwai M, Alrabiah F, et al. Epidemiology of antituberculosis drug resistance in Saudi Arabia: findings of the first national survey. Antimicrob Agents Chemother 2013;57(5):2161-6.

al-Kassimi FA, Abdullah AK, al-Hajjaj MS, al-Orainey IO, Bamgboye EA, Chowdhury MN. Nationwide community survey of tuberculosis epidemiology in Saudi Arabia. Tuber Lung Dis 1993;74(4):254-60.

Al-Orainey I, Alhedaithy MA, Alanazi AR, Barry MA, Almajid FM. Tuberculosis incidence trends in Saudi Arabia over 20 years: 1991-2010. Ann Thorac Med 2013;8(3):148-52.

Al-Orainey IO. Tuberculosis infection during Hajj pilgrimage. The risk to pilgrims and their communities. Saudi Med J 2013;34(7):676-80.

Al-Salama AA, El-Bushra HE. Head shaving practices of barbers and pilgrims to Makkah. Saudi Epidemiol Bull 1998;5:3-4.

Al-Tawfiq JA, Gautret P, Benkouiten S, Memish ZA. Mass Gatherings and the Spread of Respiratory Infections. Lessons from the Hajj. Ann Am Thorac Soc 2016;13(6):759-65.

Al-Tawfiq JA, Memish ZA. Potential risk for drug resistance globalization at the Hajj. Clin Microbiol Infect 2015;21(2):109-14.

Al Hajoj S, Varghese B, Datijan A, Shoukri M, Alzahrani A, Alkhenizan A, et al. Interferon Gamma Release Assay versus Tuberculin Skin Testing among healthcare workers of highly diverse origin in a moderate tuberculosis burden country. PLoS One 2016;11(5):e0154803.

Al Jahdali HH, Baharoon S, Abba AA, Memish ZA, Alrajhi AA, AlBarrak A, et al. Saudi guidelines for testing and treatment of latent tuberculosis infection. Ann Saudi Med 2010;30(1):38-49.

Al Wakeel JS, Makoshi Z, Al Ghonaim M, Al Harbi A, Al Suwaida A, Algahtani F, et al. The use of Quantiferon-TB gold in-tube test in screening latent tuberculosis among Saudi Arabia dialysis patients. Ann Thorac Med 2015;10(4):284-8.

AlBarrak A, Alotaibi B, Yassin Y, Mushi A, Maashi F, Seedahmed Y, et al. Proportion of adult community-acquired pneumonia cases attributable to *Streptococcus pneumoniae* among Hajj pilgrims in 2016. Int J Infect Dis 2018;69:68-74.

Aldridge RW, Yates TA, Zenner D, White PJ, Abubakar I, Hayward AC. Pre-entry screening programmes for tuberculosis in migrants to low-incidence countries: a systematic review and meta-analysis. Lancet Infect Dis 2014;14(12):1240-9.

Aleeban M, Mackey TK. Global Health and Visa Policy Reform to Address Dangers of Hajj during Summer Seasons. Front Public Health 2016;4:280.

Alele FO, Franklin RC, Emeto TI, Leggat P. Occupational tuberculosis in healthcare workers in sub-Saharan Africa: A systematic review. Arch Environ Occup Health 2018:1-14.

Aleyamma T, Chandrasekaran V, Pauline J, Vijay Baskar R, Patil A, Jain D, et al. Increased yield of smear positive pulmonary TB cases by screening patients with> 2 weeks cough, compared to> 3 weeks and adequacy of 2 sputum smear examinations for diagnosis. Indian Journal of Tuberculosis 2008;55(2):77-83.

Almutairi FM, Tayeb T, Alhakeem R, Saeed AB, Assiri A, McNabb SJN. Distribution and determinants of tuberculosis in the Kingdom of Saudi Arabia from 2005 to 2012. J Epidemiol Glob Health 2018;7 Suppl 1:S23-S8.

Alonso-Echanove J, Granich RM, Laszlo A, Chu G, Borja N, Blas R, et al. Occupational transmission of *Mycobacterium tuberculosis* to health care workers in a university hospital in Lima, Peru. Clin Infect Dis 2001;33(5):589-96.

REFERENCES

Alotaibi B, Yassin Y, Mushi A, Maashi F, Thomas A, Mohamed G, et al. Tuberculosis knowledge, attitude and practice among healthcare workers during the 2016 Hajj. PLoS One 2019;14(1):e0210913.

Alotaibi BM, Yezli S, Bin Saeed AA, Turkestani A, Alawam AH, Bieh KL. Strengthening health security at the Hajj mass gatherings: characteristics of the infectious diseases surveillance systems operational during the 2015 Hajj. J Travel Med 2017;24(3).

Altet-Gomez MN, Alcaide J, Godoy P, Romero MA, Hernandez del Rey I. Clinical and epidemiological aspects of smoking and tuberculosis: a study of 13,038 cases. Int J Tuberc Lung Dis 2005;9(4):430-6.

Alvarez-Leon EE, Espinosa-Vega E, Santana-Rodriguez E, Molina-Cabrillana JM, Perez-Arellano JL, Caminero JA, et al. Screening for tuberculosis infection in spanish healthcare workers: Comparison of the QuantiFERON-TB gold in-tube test with the tuberculin skin test. Infect Control Hosp Epidemiol 2009;30(9):876-83.

Alzeer A, Mashlah A, Fakim N, Al-Sugair N, Al-Hedaithy M, Al-Majed S, et al. Tuberculosis is the commonest cause of pneumonia requiring hospitalization during Hajj (pilgrimage to Makkah). J Infect 1998;36(3):303-6.

Alzeer AH. Respiratory tract infection during Hajj. Ann Thorac Med 2009;4(2):50-3.

Amberson JB, Riggins HM. Tuberculosis among student nurses: a five year study at Bellevue Hospital. Ann Intern Med 1936;10:156-65.

Annan A, Owusu M, Marfo KS, Larbi R, Sarpong FN, Adu-Sarkodie Y, et al. High prevalence of common respiratory viruses and no evidence of Middle East respiratory syndrome coronavirus in Hajj pilgrims returning to Ghana, 2013. Trop Med Int Health 2015;20(6):807-12.

Araj GF, Saade A, Itani LY, Avedissian AZ. Tuberculosis Burden in Lebanon: Evolution and Current Status. J Med Liban 2016;64(1):1-7.

Arbon P. Mass-gathering medicine: a review of the evidence and future directions for research. Prehosp Disaster Med 2007;22(2):131-5.

Asghar AH, Ashshi AM, Azhar EI, Bukhari SZ, Zafar TA, Momenah AM. Profile of bacterial pneumonia during Hajj. Indian J Med Res 2011;133:510-3.

Assefa D, Belachew F, Wondimagegn G, Klinkenberg E. Missed pulmonary tuberculosis: a cross sectional study in the general medical inpatient wards of a large referral hospital in Ethiopia. BMC Infect Dis 2019;19(1):60.

Awofeso N, Schelokova I, Dalhatu A. Training of front-line health workers for tuberculosis control: lessons from Nigeria and Kyrgyzstan. Hum Resour Health 2008;6:20.

Ayles H, Schaap A, Nota A, Sismanidis C, Tembwe R, De Haas P, et al. Prevalence of tuberculosis, HIV and respiratory symptoms in two Zambian communities: implications for tuberculosis control in the era of HIV. PLoS One 2009;4(5):e5602.

Babus V. Tuberculosis morbidity risk in medical nurses in specialized institutions for the treatment of lung diseases in Zagreb. Int J Tuberc Lung Dis 1997;1(3):254-8.

Bailey TC, Fraser VJ, Spitznagel EL, Dunagan WC. Risk factors for a positive tuberculin skin test among employees of an urban, midwestern teaching hospital. Ann Intern Med 1995;122(8):580-5.

Balabanova Y, Tchernyshev V, Tsigankov I, Maximova S, Mikheeva N, Fedyukovitch L, et al. Analysis of undiagnosed tuberculosis-related deaths identified at post-mortem among HIV-infected patients in Russia: a descriptive study. BMC Infect Dis 2011;11:276.

REFERENCES

Balasubramanian R, Garg R, Santha T, Gopi PG, Subramani R, Chandrasekaran V, et al. Gender disparities in tuberculosis: report from a rural DOTS programme in south India. Int J Tuberc Lung Dis 2004;8(3):323-32.

Baldwin ER. The danger of tuberculous infection in hospitals and sanatoria. United States Veterans' Bureau Medical Bulletin 1930;6:1-4.

Balkhy HH, El Beltagy K, El-Saed A, Aljasir B, Althaqafi A, Alothman AF, et al. Comparison of QuantiFERON-TB gold in tube test versus tuberculin skin test for screening of latent tuberculosis infection in Saudi Arabia: A population-based study. Ann Thorac Med 2016;11(3):197-201.

Balkhy HH, El Beltagy K, El-Saed A, Aljasir B, Althaqafi A, Alothman AF, et al. Prevalence of Latent *Mycobacterium tuberculosis* Infection (LTBI) in Saudi Arabia; Population based survey. Int J Infect Dis 2017;60:11-6.

Balkhy HH, Miller TL, Ali S, Nuzzo JB, Kentenyants K, El-Saed A, et al. Compliance with postexposure screening and treatment of latent tuberculosis infection among healthcare workers in a tertiary care hospital in Saudi Arabia. Infect Control Hosp Epidemiol 2014;35(2):176-81.

Balt E, Durrheim DN, Weyer K. Nosocomial transmission of tuberculosis to health care workers in Mpumalanga. S Afr Med J 1998;88(11):1363, 6.

Bassett IV, Wang B, Chetty S, Giddy J, Losina E, Mazibuko M, et al. Intensive tuberculosis screening for HIV-infected patients starting antiretroviral therapy in Durban, South Africa. Clin Infect Dis 2010;51(7):823-9.

Basu S, Andrews JR, Poolman EM, Gandhi NR, Shah NS, Moll A, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. Lancet 2007;370(9597):1500-7.

Bates M, Ahmed Y, Chilukutu L, Tembo J, Cheelo B, Sinyangwe S, et al. Use of the Xpert((R)) MTB/RIF assay for diagnosing pulmonary tuberculosis comorbidity and multidrug-resistant TB in obstetrics and gynaecology inpatient wards at the University Teaching Hospital, Lusaka, Zambia. Trop Med Int Health 2013;18(9):1134-40.

Bates M, Mudenda V, Shibemba A, Kaluwaji J, Tembo J, Kabwe M, et al. Burden of tuberculosis at post mortem in inpatients at a tertiary referral centre in sub-Saharan Africa: a prospective descriptive autopsy study. Lancet Infect Dis 2015;15(5):544-51.

Bates M, O'Grady J, Mwaba P, Chilukutu L, Mzyece J, Cheelo B, et al. Evaluation of the burden of unsuspected pulmonary tuberculosis and co-morbidity with non-communicable diseases in sputum producing adult inpatients. PLoS One 2012;7(7):e40774.

Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. Arch Intern Med 2007;167(4):335-42.

Baussano I, Nunn P, Williams B, Pivetta E, Bugiani M, Scano F. Tuberculosis among health care workers. Emerg Infect Dis 2011;17(3):488-94.

Behrman AJ, Shofer FS. Tuberculosis exposure and control in an urban emergency department. Ann Emerg Med 1998;31(3):370-5.

Bennett B, Carney T. Public Health Emergencies of International Concern: Global, Regional, and Local Responses to Risk. Med Law Rev 2017;25(2):223-39.

Bhebhe LT, Van Rooyen C, Steinberg WJ. Attitudes, knowledge and practices of healthcare workers regarding occupational exposure of pulmonary tuberculosis. Afr J Prim Health Care Fam Med 2014;6(1):E1-6.

Bisallah CI, Rampal L, Lye MS, Mohd Sidik S, Ibrahim N, Iliyasu Z, et al. Effectiveness of health education intervention in improving knowledge, attitude, and practices regarding Tuberculosis

among HIV patients in General Hospital Minna, Nigeria - A randomized control trial. PLoS One 2018;13(2):e0192276.
Blanc F-X, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. New England Journal of Medicine 2011;365(16):1471-81.
Blumberg HM, Sotir M, Erwin M, Bachman R, Shulman JA. Risk of house staff tuberculin skin test conversion in an area with a high incidence of tuberculosis. Clin Infect Dis 1998;27(4):826-33.
Blumberg HM, Watkins DL, Berschling JD, Antle A, Moore P, White N, et al. Preventing the nosocomial transmission of tuberculosis. Ann Intern Med 1995;122(9):658-63.
Bobrowitz ID. Active tuberculosis undiagnosed until autopsy. Am J Med 1982;72(4):650-8.
Bonifacio N, Saito M, Gilman RH, Leung F, Cordova Chavez N, Chacaltana Huarcaya J, et al. High risk for tuberculosis in hospital physicians, Peru. Emerg Infect Dis 2002;8(7):747-8.
Borgdorff MW, Floyd K, Broekmans JF. Interventions to reduce tuberculosis mortality and transmission in low- and middle-income countries. Bull World Health Organ 2002;80(3):217-27.
Borgdorff MW, Nagelkerke NJ, Dye C, Nunn P. Gender and tuberculosis: a comparison of prevalence surveys with notification data to explore sex differences in case detection. Int J Tuberc Lung Dis 2000;4(2):123-32.
Boudreau AY, Baron SL, Steenland NK, Van Gilder TJ, Decker JA, Galson SK, et al. Occupational risk of Mycobacterium tuberculosis infection in hospital workers. Am J Ind Med 1997;32(5):528-34.
Boynton RE. The incidence of tuberculosis infection in student nurses. Am Rev Tuberc 1939;39:671-4.
Brandy L. Tuberculosis in hospital personnel. JAMA 1940;114:102-5.
Brunet L, Pai M, Davids V, Ling D, Paradis G, Lenders L, et al. High prevalence of smoking among patients with suspected tuberculosis in South Africa. Eur Respir J 2011;38(1):139-46.
Buchan J, Dal Poz MR. Skill mix in the health care workforce: reviewing the evidence. Bull World Health Organ 2002;80(7):575-80.
Bukhary ZA, Amer SM, Emara MM, Abdalla ME, Ali SA. Screening of latent tuberculosis infection among health care workers working in Hajj pilgrimage area in Saudi Arabia, using interferon gamma release assay and tuberculin skin test. Ann Saudi Med 2018;38(2):90-6.
Buregyeya E, Kasasa S, Mitchell EM. Tuberculosis infection control knowledge and attitudes among health workers in Uganda: a cross-sectional study. BMC Infect Dis 2016;16(1):416.
Casas I, Latorre I, Esteve M, Ruiz-Manzano J, Rodriguez D, Prat C, et al. Evaluation of interferon-gamma release assays in the diagnosis of recent tuberculosis infection in health care workers. PLoS One 2009;4(8):e6686.
Casey TP. Fatal undiagnosed tuberculosis. N Z Med J 1966;65(410):672-8.
Casey TP. Undiagnosed fatal tuberculosis. N Z Med J 1968;67(431):492-3.
Cegielski J, McMurray D. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. The international journal of tuberculosis and lung disease 2004;8(3):286-98.
Centers for Disease C, Prevention. Exposure of passengers and flight crew to *Mycobacterium tuberculosis* on commercial aircraft, 1992-1995. MMWR Morb Mortal Wkly Rep 1995;44(8):137-40.
Centers for Disease Control and Prevention. TB Elimination: BCG Vaccine. 2012.

REFERENCES

Chang K, Lu W, Wang J, Zhang K, Jia S, Li F, et al. Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: a meta-analysis. J Infect 2012;64(6):580-8.

Chang SH, Cataldo JK. A systematic review of global cultural variations in knowledge, attitudes and health responses to tuberculosis stigma. Int J Tuberc Lung Dis 2014;18(2):168-73, i-iv.

Chen TC, Lu PL, Lin WR, Lin CY, Lin SH, Lin CJ, et al. Diagnosis and treatment of pulmonary tuberculosis in hospitalized patients are affected by physician specialty and experience. Am J Med Sci 2010;340(5):367-72.

China Tuberculosis Control C. The effect of tuberculosis control in China. Lancet 2004;364(9432):417-22.

Choi JC, Shin JW, Kim JY, Park IW, Choi BW, Lee MK. The effect of previous tuberculin skin test on the follow-up examination of whole-blood interferon-gamma assay in the screening for latent tuberculosis infection. Chest 2008;133(6):1415-20.

Christie CD, Constantinou P, Marx ML, Willke MJ, Marot K, Mendez FL, et al. Low risk for tuberculosis in a regional pediatric hospital: nine-year study of community rates and the mandatory employee tuberculin skin-test program. Infect Control Hosp Epidemiol 1998;19(3):168-74.

Christopher DJ, Shankar D, Datey A, Zwerling A, Pai M. Safety of the two-step tuberculin skin test in Indian health care workers. Int J Mycobacteriol 2014;3(4):247-51.

Chuck C, Robinson E, Macaraig M, Alexander M, Burzynski J. Enhancing management of tuberculosis treatment with video directly observed therapy in New York City. The International Journal of Tuberculosis and Lung Disease 2016;20(5):588-93.

Cobelens FG, van Deutekom H, Draayer-Jansen IW, Schepp-Beelen AC, van Gerven PJ, van Kessel RP, et al. Risk of infection with *Mycobacterium tuberculosis* in travellers to areas of high tuberculosis endemicity. Lancet 2000;356(9228):461-5.

Codlin AJ, Khowaja S, Chen Z, Rahbar MH, Qadeer E, Ara I, et al. Short report: Gender differences in tuberculosis notification in Pakistan. Am J Trop Med Hyg 2011;85(3):514-7.

Cohen T, Murray M, Wallengren K, Alvarez GG, Samuel EY, Wilson D. The prevalence and drug sensitivity of tuberculosis among patients dying in hospital in KwaZulu-Natal, South Africa: a postmortem study. PLoS Med 2010;7(6):e1000296.

Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol 1974;99(2):131-8.

Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. Lancet 2010;376(9748):1244-53.

Craven RB, Wenzel RP, Atuk N. Minimizing tuberculosis risk to hospital personnel and students exposed to unsuspected disease. Ann Intern Med 1975;82(5):628-32.

Creswell J, Raviglione M, Ottmani S, Migliori GB, Uplekar M, Blanc L, et al. Tuberculosis and noncommunicable diseases: neglected links and missed opportunities. Eur Respir J 2011;37(5):1269-82.

Cuhadaroglu C, Erelel M, Tabak L, Kilicaslan Z. Increased risk of tuberculosis in health care workers: a retrospective survey at a teaching hospital in Istanbul, Turkey. BMC Infect Dis 2002;2:14.

Cuneo WD, Snider DE, Jr. Enhancing patient compliance with tuberculosis therapy. Clin Chest Med 1989;10(3):375-80.

Daniels M. Primary tuberculosis infection in nurses. [Summary of the Prophit Survey]. Lancet 1944:165-70.

REFERENCES

Daniels M, Ridehalgh F, Springett VH, Hall IM. Tuberculosis in young adults: Report on the Prophit Tuberculosis Survey, 1936-1944. London: HK Lewis and Co, Ltd; 1948 1948.

Daulay RS, Majeda A, Nataprawira HM. Unrecognized and delayed to diagnose of adolescence tuberculosis case in a boarding school in West Java, Indonesia. Int J Mycobacteriol 2018;7(4):387-9.

Davies JC. Silicosis and tuberculosis among South African goldminers--an overview of recent studies and current issues. S Afr Med J 2001;91(7):562-6.

Davies PD. Risk factors for tuberculosis. Monaldi Arch Chest Dis 2005;63(1):37-46.

De Lorenzo RA. Mass gathering medicine: a review. Prehosp Disaster Med 1997;12(1):68-72.

de Souza FM, do Prado TN, Pinheiro Jdos S, Peres RL, Lacerda TC, Loureiro RB, et al. Comparison of interferon-gamma release assay to two cut-off points of tuberculin skin test to detect latent *Mycobacterium tuberculosis* infection in primary health care workers. PLoS One 2014;9(8):e102773.

Demissie Gizaw G, Aderaw Alemu Z, Kibret KT. Assessment of knowledge and practice of health workers towards tuberculosis infection control and associated factors in public health facilities of Addis Ababa, Ethiopia: A cross-sectional study. Arch Public Health 2015;73(1):15.

Deribew A, Abebe G, Apers L, Abdissa A, Deribe F, Woldemichael K, et al. Prevalence of pulmonary TB and spoligotype pattern of Mycobacterium tuberculosis among TB suspects in a rural community in Southwest Ethiopia. BMC Infect Dis 2012;12:54.

Deris ZZ, Hasan H, Sulaiman SA, Wahab MS, Naing NN, Othman NH. The prevalence of acute respiratory symptoms and role of protective measures among Malaysian hajj pilgrims. J Travel Med 2010;17(2):82-8.

Dharmadhikari AS, Mphahlele M, Stoltz A, Venter K, Mathebula R, Masotla T, et al. Surgical face masks worn by patients with multidrug-resistant tuberculosis: impact on infectivity of air on a hospital ward. Am J Respir Crit Care Med 2012;185(10):1104-9.

Dhungana GP, Sharma S, Khadga P, Verma SC. Surveillance of tuberculosis among HIV infected persons in three different regions of Nepal. Nepal Med Coll J 2013;15(2):113-6.

Dielman M, Harmmeijer JM. Improving health worker performance: in search of promising practices. KIT – Royal Tropical Institute; The Netherlands2006.

Dimitrova B, Hutchings A, Atun R, Drobniewski F, Marchenko G, Zakharova S, et al. Increased risk of tuberculosis among health care workers in Samara Oblast, Russia: analysis of notification data. Int J Tuberc Lung Dis 2005;9(1):43-8.

Do AN, Limpakarnjarat K, Uthaivoravit W, Zuber PL, Korattana S, Binkin N, et al. Increased risk of *Mycobacterium tuberculosis* infection related to the occupational exposures of health care workers in Chiang Rai, Thailand. Int J Tuberc Lung Dis 1999;3(5):377-81.

Dodor EA, Afenyadu GY. Factors associated with tuberculosis treatment default and completion at the Effia-Nkwanta Regional Hospital in Ghana. Trans R Soc Trop Med Hyg 2005;99(11):827-32.

Dodor EA, Kelly SJ. Manifestations of tuberculosis stigma within the healthcare system: the case of Sekondi-Takoradi Metropolitan district in Ghana. Health Policy 2010;98(2-3):195-202.

Dodor EA, Neal K, Kelly S. An exploration of the causes of tuberculosis stigma in an urban district in Ghana. Int J Tuberc Lung Dis 2008;12(9):1048-54.

Dogar OF, Shah SK, Chughtai AA, Qadeer E. Gender disparity in tuberculosis cases in eastern and western provinces of Pakistan. BMC Infect Dis 2012;12:244.

REFERENCES

Dooley SW, Villarino ME, Lawrence M, Salinas L, Amil S, Rullan JV, et al. Nosocomial transmission of tuberculosis in a hospital unit for HIV-infected patients. JAMA 1992;267(19):2632-4.

Doosti Irani A, Hashemi Shahraki A, Ghaderi E, Nasehi M, Mostafavi E. Lack of optimum practice among health care workers regarding tuberculosis in Iran: A knowledge, attitude, and practice study. Am J Infect Control 2015;43(5):e7-12.

du Preez K, Mandalakas AM, Kirchner HL, Grewal HM, Schaaf HS, van Wyk SS, et al. Environmental tobacco smoke exposure increases Mycobacterium tuberculosis infection risk in children. Int J Tuberc Lung Dis 2011;15(11):1490-6, i.

Dublin LI. Incidence of tuberculosis among physicians and nurses. Journal of the Outdoor Life 1914:204-5.

Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999;282(7):677-86.

Dye C, Williams BG. The population dynamics and control of tuberculosis. Science 2010;328(5980):856-61.

Ebrahim SH, Memish ZA, Uyeki TM, Khoja TA, Marano N, McNabb SJ. Public health. Pandemic H1N1 and the 2009 Hajj. Science 2009;326(5955):938-40.

Ehrenkranz NJ, Kicklighter JL. Tuberculosis outbreak in a general hospital: evidence for airborne spread of infection. Ann Intern Med 1972;77(3):377-82.

El-Helaly M, Khan W, El-Saed A, Balkhy HH. Pre-employment screening of latent tuberculosis infection among healthcare workers using tuberculin skin test and QuantiFERON-TB Gold test at a tertiary care hospital in Saudi Arabia. J Infect Public Health 2014;7(6):481-8.

El-Sheikh SM, El-Assouli SM, Mohammed KA, Albar M. Bacteria and viruses that cause respiratory tract infections during the pilgrimage (Haj) season in Makkah, Saudi Arabia. Trop Med Int Health 1998;3(3):205-9.

Elhassan MM, Hemeg HA, Elmekki MA, Turkistani KA, Abdul-Aziz AA. Burden of multidrug resistant *Mycobacterium tuberculosis* among new cases in Al-Madinah Al-Monawarah, Saudi Arabia. Infect Disord Drug Targets 2017;17(1):14-23.

Elmadhoun WM, Noor SK, Bushara SO, Ahmed EO, Mustafa H, Sulaiman AA, et al. Epidemiology of tuberculosis and evaluation of treatment outcomes in the national tuberculosis control programme, River Nile state, Sudan, 2011-2013. East Mediterr Health J 2016;22(2):95-102.

Engelbrecht M, Janse van Rensburg A, Kigozi G, van Rensburg HD. Factors associated with good TB infection control practices among primary healthcare workers in the Free State Province, South Africa. BMC Infect Dis 2016;16(1):633.

Escombe A, Huaroto L, Ticona E, Burgos M, Sanchez I, Carrasco L, et al. Tuberculosis transmission risk and infection control in a hospital emergency department in Lima, Peru. The international journal of tuberculosis and lung disease 2010;14(9):1120-6.

Escombe AR, Oeser CC, Gilman RH, Navincopa M, Ticona E, Pan W, et al. Natural ventilation for the prevention of airborne contagion. PLoS Med 2007;4(2):e68.

Eyob G, Gebeyhu M, Goshu S, Girma M, Lemma E, Fontanet A. Increase in tuberculosis incidence among the staff working at the Tuberculosis Demonstration and Training Centre in Addis Ababa, Ethiopia: a retrospective cohort study (1989-1998). Int J Tuberc Lung Dis 2002;6(1):85-8.

REFERENCES

Falzon D, Jaramillo E, Schünemann H, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. European Respiratory Journal 2011:erj00736-2011.

Falzon D, Jaramillo E, Wares F, Zignol M, Floyd K, Raviglione MC. Universal access to care for multidrug-resistant tuberculosis: an analysis of surveillance data. Lancet Infect Dis 2013;13(8):690-7.

Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. European Respiratory Journal 2017;49(3):1602308.

Farley JE, Tudor C, Mphahlele M, Franz K, Perrin NA, Dorman S, et al. A national infection control evaluation of drug-resistant tuberculosis hospitals in South Africa. Int J Tuberc Lung Dis 2012;16(1):82-9.

Fatima R, Harris RJ, Enarson DA, Hinderaker SG, Qadeer E, Ali K, et al. Estimating tuberculosis burden and case detection in Pakistan. Int J Tuberc Lung Dis 2014;18(1):55-60.

Ferreira Junior S, Oliveira HB, Marin-Leon L. [Knowledge, attitudes and practices on tuberculosis in prisons and public health services]. Rev Bras Epidemiol 2013;16(1):100-13.

Fica CA, Cifuentes DM, Ajenjo HM, Jemenao PM, Zambrano OA, Febre VN, et al. Tuberculosis in healthcare workers. Rev Chilena Infectol 2008;25(4):243-55.

Finnie RK, Khoza LB, van den Borne B, Mabunda T, Abotchie P, Mullen PD. Factors associated with patient and health care system delay in diagnosis and treatment for TB in sub-Saharan African countries with high burdens of TB and HIV. Trop Med Int Health 2011;16(4):394-411.

Fox BD, Kramer MR, Mor Z, Preiss R, Rusanov V, Fuks L, et al. The QuantiFERON-TB-GOLD assay for tuberculosis screening in healthcare workers: a cost-comparison analysis. Lung 2009;187(6):413-9.

Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J 2013;41(1):140-56.

Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999;3(10 Suppl 2):S231-79.

Fraser VJ, Kilo CM, Bailey TC, Medoff G, Dunagan WC. Screening of physicians for tuberculosis. Infect Control Hosp Epidemiol 1994;15(2):95-100.

Freeman JT, Marshall RJ, Newton S, Austin P, Taylor S, Chew TC, et al. Screening for Mycobacterium tuberculosis infection among healthcare workers in New Zealand: prospective comparison between the tuberculin skin test and the QuantiFERON-TB Gold In-Tube assay. N Z Med J 2012;125(1349):21-9.

Fridkin SK, Manangan L, Bolyard E, Jarvis WR. SHEA-CDC TB survey, Part II: Efficacy of TB infection control programs at member hospitals, 1992. Society for Healthcare Epidemiology of America. Infect Control Hosp Epidemiol 1995;16(3):135-40.

Gallardo CR, Rigau Comas D, Valderrama Rodríguez A, Roqué i Figuls M, Parker LA, Caylà J, et al. Fixed-dose combinations of drugs versus single drug formulations for treating pulmonary tuberculosis. Cochrane Database of Systematic Reviews 2012;7.

Garcia-Garcia JM, Rodrigo T, Casals M, Ruiz-Manzano J, Pascual-Pascual T, Cayla JA. Spanish Compliance With Guidelines for Prescribing Four Drugs in the Intensive Phase of Standard Tuberculosis Treatment. Arch Bronconeumol 2016;52(5):262-8.

REFERENCES

Garcia-Garcia ML, Jimenez-Corona A, Jimenez-Corona ME, Ferreyra-Reyes L, Martinez K, Rivera-Chavira B, et al. Factors associated with tuberculin reactivity in two general hospitals in Mexico. Infect Control Hosp Epidemiol 2001;22(2):88-93.

Gatrad AR, Sheikh A. Hajj and risk of blood borne infections. Arch Dis Child 2001;84(4):375.

Gatrad AR, Sheikh A. Hajj: journey of a lifetime. BMJ 2005;330(7483):133-7.

Gautret P, Benkouiten S, Griffiths K, Sridhar S. The inevitable Hajj cough: Surveillance data in French pilgrims, 2012-2014. Travel Med Infect Dis 2015;13(6):485-9.

Gautret P, Charrel R, Benkouiten S, Belhouchat K, Nougairede A, Drali T, et al. Lack of MERS coronavirus but prevalence of influenza virus in French pilgrims after 2013 Hajj. Emerg Infect Dis 2014;20(4):728-30.

Gautret P, Soula G, Delmont J, Parola P, Brouqui P. Common health hazards in French pilgrims during the Hajj of 2007: a prospective cohort study. J Travel Med 2009;16(6):377-81.

Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. The Lancet Infectious Diseases 2017;17(2):223-34.

Gelaw SM. Socioeconomic Factors Associated with Knowledge on Tuberculosis among Adults in Ethiopia. Tuberc Res Treat 2016;2016:6207457.

General Directorate of Infection Prevention and Control. The committee for infection prevention and control 2017 Hajj report. Kingdom of Saudi Arabia2017.

Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J 2015;46(6):1563-76.

Ghabrah TM, Madani TA, Albarrak AM, Alhazmi MA, Alazraqi TA, Alhudaithi MA, et al. Assessment of infection control knowledge, attitude and practice among healthcare workers during the Hajj period of the Islamic year 1423 (2003). Scand J Infect Dis 2007;39(11-12):1018-24.

Ghaznawi HI, Khalil MH. Health hazards and risk factors in the 1406 H (1986 G) Hajj season. Saudi Med J 1988;9(3):274-82.

Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. New England Journal of Medicine 2014;371(17):1577-87.

Girardi E, Angeletti C, Puro V, Sorrentino R, Magnavita N, Vincenti D, et al. Estimating diagnostic accuracy of tests for latent tuberculosis infection without a gold standard among healthcare workers. Euro Surveill 2009;14(43).

Gleason JA, McNabb SJ, Abduljadayel N, Abouzeid MS, Memish ZA. Tuberculosis trends in the Kingdom of Saudi Arabia, 2005 to 2009. Ann Epidemiol 2012;22(4):264-9.

Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. New England Journal of Medicine 2012;366(23):2151-60.

Godoy P, Cayla JA, Carmona G, Camps N, Alvarez J, Alseda M, et al. Smoking in tuberculosis patients increases the risk of infection in their contacts. Int J Tuberc Lung Dis 2013;17(6):771-6.

Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician 2005;72(9):1761-8.

Golub JE, Bur S, Cronin WA, Gange S, Baruch N, Comstock GW, et al. Patient and health care system delays in pulmonary tuberculosis diagnosis in a low-incidence state. Int J Tuberc Lung Dis 2005;9(9):992-8.

REFERENCES

Golub JE, Bur S, Cronin WA, Gange S, Baruch N, Comstock GW, et al. Delayed tuberculosis diagnosis and tuberculosis transmission. Int J Tuberc Lung Dis 2006;10(1):24-30.

Gopinath KG, Siddique S, Kirubakaran H, Shanmugam A, Mathai E, Chandy GM. Tuberculosis among healthcare workers in a tertiary-care hospital in South India. J Hosp Infect 2004;57(4):339-42.

Gordon SV, Parish T. Microbe Profile: Mycobacterium tuberculosis: Humanity's deadly microbial foe. Microbiology 2018;164(4):437-9.

Greenaway C, Menzies D, Fanning A, Grewal R, Yuan L, FitzGerald JM, et al. Delay in diagnosis among hospitalized patients with active tuberculosis--predictors and outcomes. Am J Respir Crit Care Med 2002;165(7):927-33.

Gumusboga A, Aung KJ, Rigouts L, Van Deun A. Transmission of multidrug-resistant and extensively drug-resistant tuberculosis in rural Bangladesh: lessons learnt. Public Health Action 2012;2(3):76-8.

Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS 2015;29(15):1987-2002.

Habicht JP, Victora CG, Vaughan JP. Evaluation designs for adequacy, plausibility and probability of public health programme performance and impact. Int J Epidemiol 1999;28(1):10-8.

Harries AD, Hargreaves NJ, Gausi F, Kwanjana JH, Salaniponi FM. Preventing tuberculosis among health workers in Malawi. Bull World Health Organ 2002;80(7):526-31.

Harries AD, Kamenya A, Namarika D, Msolomba IW, Salaniponi FM, Nyangulu DS, et al. Delays in diagnosis and treatment of smear-positive tuberculosis and the incidence of tuberculosis in hospital nurses in Blantyre, Malawi. Trans R Soc Trop Med Hyg 1997;91(1):15-7.

Harries AD, Nyirenda TE, Banerjee A, Boeree MJ, Salaniponi FM. Tuberculosis in health care workers in Malawi. Trans R Soc Trop Med Hyg 1999;93(1):32-5.

Harris RC, Grandjean L, Martin LJ, Miller AJ, Nkang JE, Allen V, et al. The effect of early versus late treatment initiation after diagnosis on the outcomes of patients treated for multidrug-resistant tuberculosis: a systematic review. BMC Infect Dis 2016;16:193.

Harris RC, Khan MS, Martin LJ, Allen V, Moore DA, Fielding K, et al. The effect of surgery on the outcome of treatment for multidrug-resistant tuberculosis: a systematic review and meta-analysis. BMC infectious diseases 2016;16(1):262.

Hashem AM, Al-Subhi TL, Badroon NA, Hassan AM, Bajrai LHM, Banassir TM, et al. MERS-CoV , influenza and other respiratory viruses among symptomatic pilgrims during 2014 Hajj season. J Med Virol 2019.

Hashim DS, Al Kubaisy W, Al Dulayme A. Knowledge, attitudes and practices survey among health care workers and tuberculosis patients in Iraq. East Mediterr Health J 2003;9(4):718-31.

Hatzenbuehler LA, Starke JR, Smith EO, Turner TL, Balmer DF, Arif Z, et al. Increased adolescent knowledge and behavior following a one-time educational intervention about tuberculosis. Patient Educ Couns 2017;100(5):950-6.

Havlir DV, Kendall MA, Ive P, Kumwenda J, Swindells S, Qasba SS, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. New England Journal of Medicine 2011;365(16):1482-91.

He G, Li Y, Zhao F, Wang L, Cheng S, Guo H, et al. The Prevalence and Incidence of Latent Tuberculosis Infection and Its Associated Factors among Village Doctors in China. PLoS One 2015;10(5):e0124097.

REFERENCES

He GX, van denHof S, van der Werf MJ, Wang GJ, Ma SW, Zhao DY, et al. Infection control and the burden of tuberculosis infection and disease in health care workers in china: a cross-sectional study. BMC Infect Dis 2010;10:313.

He GX, Wang LX, Chai SJ, Klena JD, Cheng SM, Ren YL, et al. Risk factors associated with tuberculosis infection among health care workers in Inner Mongolia, China. Int J Tuberc Lung Dis 2012;16(11):1485-91.

Heimbeck J. Immunity to tuberculosis. Arch Intern Med 1928;41:336-42.

Heimbeck J. Tuberculosis in hospital nurses. Tubercle 1936;18:97-9.

Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, et al. Rapid detection of *Mycobacterium tuberculosis* and rifampin resistance by use of on-demand, near-patient technology. J Clin Microbiol 2010;48(1):229-37.

Ho J, Byrne AL, Linh NN, Jaramillo E, Fox GJ. Decentralized care for multidrug-resistant tuberculosis: a systematic review and meta-analysis. Bulletin of the World Health Organization 2017;95(8):584-93.

Hoa NB, Sy DN, Nhung NV, Tiemersma EW, Borgdorff MW, Cobelens FG. National survey of tuberculosis prevalence in Vietnam. Bull World Health Organ 2010;88(4):273-80.

Hoa NP, Diwan VK, Thorson AE. Diagnosis and treatment of pulmonary tuberculosis at basic health care facilities in rural Vietnam: a survey of knowledge and reported practices among health staff. Health Policy 2005;72(1):1-8.

Hochberg NS, Sarkar S, Horsburgh CR, Jr., Knudsen S, Pleskunas J, Sahu S, et al. Comorbidities in pulmonary tuberculosis cases in Puducherry and Tamil Nadu, India: Opportunities for intervention. PLoS One 2017;12(8):e0183195.

Hoffman SJ, Guindon GE, Lavis JN, Randhawa H, Becerra-Posada F, Dejman M, et al. Surveying the knowledge and practices of health professionals in China, India, Iran, and Mexico on treating tuberculosis. Am J Trop Med Hyg 2016;94(5):959-70.

Hong YP, Kwon DW, Kim SJ, Chang SC, Kang MK, Lee EP, et al. Survey of knowledge, attitudes and practices for tuberculosis among general practitioners. Tuber Lung Dis 1995;76(5):431-5.

Horai Z. Pulmonary tuberculosis and pneumoconiosis. Kekkaku 1975;50(11):600-2.

Hosoglu S, Tanrikulu AC, Dagli C, Akalin S. Tuberculosis among health care workers in a short working period. Am J Infect Control 2005;33(1):23-6.

Hotta K, Ogura T, Nishii K, Kodani T, Onishi M, Shimizu Y, et al. Whole blood interferon-gamma assay for baseline tuberculosis screening among Japanese healthcare students. PLoS One 2007;2(8):e803.

Houts PS, Doak CC, Doak LG, Loscalzo MJ. The role of pictures in improving health communication: a review of research on attention, comprehension, recall, and adherence. Patient Educ Couns 2006;61(2):173-90.

Institute of Medicine. Tuberculosis in the Workplace. Washington, DC2001.

Isara AR, Akpodiete A. Concerns about the knowledge and attitude of multidrug-resistant tuberculosis among health care workers and patients in Delta State, Nigeria. Niger J Clin Pract 2015;18(5):664-9.

Islam S. Latent tuberculosis infection among healthcare workers in chest disease hospitals, Bangladesh. Health and Science Bulletin 2014;12(1):1-7.

Jadgal KM, Nakhaei-Moghadam T, Alizadeh-Seiouki H, Zareban I, Sharifi-Rad J. Impact of Educational Intervention on Patients Behavior with Smear-positive Pulmonary Tuberculosis: A Study Using the Health Belief Model. Mater Sociomed 2015;27(4):229-33.

REFERENCES

Jaiswal A, Singh V, Ogden JA, Porter JD, Sharma PP, Sarin R, et al. Adherence to tuberculosis treatment: lessons from the urban setting of Delhi, India. Trop Med Int Health 2003;8(7):625-33.

Jaramillo E. Guidelines for the programmatic management of drug-resistant tuberculosis: World Health Organization, 2008.

Jarand J, Shean K, O'Donnell M, Loveday M, Kvasnovsky C, Van der Walt M, et al. Extensively drug-resistant tuberculosis (XDR-TB) among health care workers in South Africa. Trop Med Int Health 2010;15(10):1179-84.

Jarvis WR. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis*. Am J Infect Control 1995;23(2):146-51.

Jelip J, Mathew GG, Yusin T, Dony JF, Singh N, Ashaari M, et al. Risk factors of tuberculosis among health care workers in Sabah, Malaysia. Tuberculosis (Edinb) 2004;84(1-2):19-23.

Jensen PA, Lambert LA, Iademarco MF, Ridzon R, Cdc. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. MMWR Recomm Rep 2005;54(RR-17):1-141.

Jereb J, Etkind SC, Joglar OT, Moore M, Taylor Z. Tuberculosis contact investigations: outcomes in selected areas of the United States, 1999. Int J Tuberc Lung Dis 2003;7(12 Suppl 3):S384-90.

Jiamjarasrangsi W, Hirunsuthikul N, Kamolratanakul P. Tuberculosis among health care workers at King Chulalongkorn Memorial Hospital, 1988-2002. Int J Tuberc Lung Dis 2005;9(11):1253-8.

Jindani A, Harrison TS, Nunn AJ, Phillips PP, Churchyard GJ, Charalambous S, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. New England Journal of Medicine 2014;371(17):1599-608.

Jo KW. Preventing the Transmission of Tuberculosis in Health Care Settings: Administrative Control. Tuberc Respir Dis (Seoul) 2017;80(1):21-6.

Jo KW, Hong Y, Park JS, Bae IG, Eom JS, Lee SR, et al. Prevalence of Latent Tuberculosis Infection among Health Care Workers in South Korea: A Multicenter Study. Tuberc Respir Dis (Seoul) 2013;75(1):18-24.

Johnson JE, Johnson JE, Jr. The hazard of undiagnosed tuberculosis in general hospitals; a five hospital survey. Tex State J Med 1959;55(6):427-30.

Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PloS one 2009;4(9):e6914.

Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. PLoS Med 2006;3(12):e494.

Jung DH, Jo KW, Shim TS. Prevalence of Latent Tuberculosis Infection among Medical Students in South Korea. Tuberc Respir Dis (Seoul) 2012;73(4):219-23.

Jurcev-Savicevic A, Mulic R, Ban B, Kozul K, Bacun-Ivcek L, Valic J, et al. Risk factors for pulmonary tuberculosis in Croatia: a matched case-control study. BMC Public Health 2013;13:991.

Juul A. Clinically undiagnosed active tuberculosis. Experience from an autopsy material. Acta Med Scand 1977;202(3):225-9.

Kanjee Z, Catterick K, Moll AP, Amico KR, Friedland GH. Tuberculosis infection control in rural South Africa: survey of knowledge, attitude and practice in hospital staff. J Hosp Infect 2011;79(4):333-8.

Kanyerere HS, Salaniponi FM. Tuberculosis in health care workers in a central hospital in Malawi. Int J Tuberc Lung Dis 2003;7(5):489-92.

REFERENCES

Kaona FA, Tuba M, Siziya S, Sikaona L. An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment. BMC Public Health 2004;4:68.

Kapata N, Chanda-Kapata P, Ngosa W, Metitiri M, Klinkenberg E, Kalisvaart N, et al. The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013-2014. PLoS One 2016;11(1):e0146392.

Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Harrison's principles of internal medicine, 19e. 2015.

Kassim S, Zuber P, Wiktor SZ, Diomande FV, Coulibaly IM, Coulibaly D, et al. Tuberculin skin testing to assess the occupational risk of Mycobacterium tuberculosis infection among health care workers in Abidjan, Cote d'Ivoire. Int J Tuberc Lung Dis 2000;4(4):321-6.

Katz I, Rosenthal T, Michaeli D. Undiagnosed tuberculosis in hospitalized patients. Chest 1985;87(6):770-4.

Kayanja HK, Debanne S, King C, Whalen CC. Tuberculosis infection among health care workers in Kampala, Uganda. Int J Tuberc Lung Dis 2005;9(6):686-8.

Kebede AH, Alebachew Z, Tsegaye F, Lemma E, Abebe A, Agonafir M, et al. The first population-based national tuberculosis prevalence survey in Ethiopia, 2010-2011. Int J Tuberc Lung Dis 2014;18(6):635-9.

Kenyon C, Zondo S. Why do some South African ethnic groups have very high HIV rates and others not? Afr J AIDS Res 2011;10(1):51-62.

Kenyon TA, Valway SE, Ihle WW, Onorato IM, Castro KG. Transmission of multidrug-resistant Mycobacterium tuberculosis during a long airplane flight. N Engl J Med 1996;334(15):933-8.

Keskiner R, Ergonul O, Demiroglu Z, Eren S, Baykam N, Dokuzoguz B. Risk of tuberculous infection among healthcare workers in a tertiary-care hospital in Ankara, Turkey. Infect Control Hosp Epidemiol 2004;25(12):1067-71.

Khan AA, Noji EK. Hajj stampede disaster, 2015: Reflections from the frontlines. Am J Disaster Med 2016;11(1):59-68.

Khan AH, Israr M, Khan A, Aftab RA, Khan TM. Smoking on treatment outcomes among tuberculosis patients. Am J Med Sci 2015;349(6):505-9.

Khan NA, Ishag AM, Ahmad MS, El-Sayed FM, Bachal ZA, Abbas TG. Pattern of medical diseases and determinants of prognosis of hospitalization during 2005 Muslim pilgrimage Hajj in a tertiary care hospital. A prospective cohort study. Saudi Med J 2006;27(9):1373-80.

Khoury NZ, Binnicker MJ, Wengenack NL, Aksamit TR, Buchta WG, Molella RG. Preemployment screening for tuberculosis in a large health care setting: comparison of the tuberculin skin test and a whole-blood interferon-gamma release assay. J Occup Environ Med 2011;53(3):290-3.

Kiefer EM, Shao T, Carrasquillo O, Nabeta P, Seas C. Knowledge and attitudes of tuberculosis management in San Juan de Lurigancho district of Lima, Peru. J Infect Dev Ctries 2009;3(10):783-8.

Kigozi NG, Heunis JC, Engelbrecht MC, Janse van Rensburg AP, van Rensburg H. Tuberculosis knowledge, attitudes and practices of patients at primary health care facilities in a South African metropolitan: research towards improved health education. BMC Public Health 2017;17(1):795.

Kilale A, Godfather K, Amos K, Mabuba C, Bernard N, William M, et al. High prevalence of tuberculosis diagnosed during autopsy examination at Muhimbili National Hospital in Dar es Salaam, Tanzania. Tanzania Journal of Health Research 2013;15(3):1-18.

REFERENCES

Kilinc O, Ucan ES, Cakan MD, Ellidokuz MD, Ozol MD, Sayiner A, et al. Risk of tuberculosis among healthcare workers: can tuberculosis be considered as an occupational disease? Respir Med 2002;96(7):506-10.

Kolappan C, Gopi PG. Tobacco smoking and pulmonary tuberculosis. Thorax 2002;57(11):964-6.

Kraiger K, Ford JK, Salas E. Application of cognitive, skill-based, and affective theories of learning outcomes to new methods of training evaluation. J Appl Psychol 1993;78:311–28.

Krishnan L, Akande T, Shankar AV, McIntire KN, Gounder CR, Gupta A, et al. Gender-related barriers and delays in accessing tuberculosis diagnostic and treatment services: a systematic review of qualitative studies. Tuberc Res Treat 2014;2014:215059.

Kruuner A, Danilovitsh M, Pehme L, Laisaar T, Hoffner SE, Katila ML. Tuberculosis as an occupational hazard for health care workers in Estonia. Int J Tuberc Lung Dis 2001;5(2):170-6.

Kuaban C, Noeske J, Rieder H, Aït-Khaled N, Abena Foe J, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. The International Journal of Tuberculosis and Lung Disease 2015;19(5):517-24.

Kufa T, Mngomezulu V, Charalambous S, Hanifa Y, Fielding K, Grant AD, et al. Undiagnosed tuberculosis among HIV clinic attendees: association with antiretroviral therapy and implications for intensified case finding, isoniazid preventive therapy, and infection control. Journal of acquired immune deficiency syndromes (1999) 2012;60(2):e22-8.

La Torre G, Scalingi S, Garruto V, Siclari M, Chiarini M, Mannocci A. Knowledge, attitude and behaviours towards recommended vaccinations among healthcare workers. Healthcare (Basel) 2017;5(1).

Lai KK, Fontecchio SA, Kelley AL, Melvin ZS. Knowledge of the transmission of tuberculosis and infection control measures for tuberculosis among healthcare workers. Infect Control Hosp Epidemiol 1996;17(3):168-70.

Lamberti M, Uccello R, Monaco MGL, Muoio M, Feola D, Sannolo N, et al. Tuberculin skin test and Quantiferon test agreement and influencing factors in tuberculosis screening of healthcare workers: a systematic review and meta-analysis. J Occup Med Toxicol 2015;10:2.

Langendam MW, van der Werf MJ, Huitric E, Manissero D. Prevalence of inappropriate tuberculosis treatment regimens: a systematic review. Eur Respir J 2012;39(4):1012-20.

Laohasiriwong W, Mahato RK, Koju R, Vaeteewootacharn K. Delay for First Consultation and Its Associated Factors among New Pulmonary Tuberculosis Patients of Central Nepal. Tuberc Res Treat 2016;2016:4583871.

Larcher C, Frizzera E, Pretto P, Lang M, Sonnleitner N, Huemer HP. Immunosurveillance for *Mycobacterium tuberculosis* of health care personnel in a third level care hospital. Med Lav 2012;103(1):26-36.

Larsen NM, Biddle CL, Sotir MJ, White N, Parrott P, Blumberg HM. Risk of tuberculin skin test conversion among health care workers: occupational versus community exposure and infection. Clin Infect Dis 2002;35(7):796-801.

Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A, Vogt M, et al. Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. PLoS Med 2011;8(7):e1001067.

Laxminarayan R, Klein EY, Darley S, Adeyi O. Global investments in TB control: economic benefits. Health Aff (Millwood) 2009;28(4):w730-42.

Lee JK, Ng TH. Undiagnosed tuberculosis in hospitalized patients--an autopsy survey. J R Soc Health 1990;110(4):141-3.

REFERENCES

Lee K, Han MK, Choi HR, Choi CM, Oh YM, Lee SD, et al. Annual incidence of latent tuberculosis infection among newly employed nurses at a tertiary care university hospital. Infect Control Hosp Epidemiol 2009;30(12):1218-22.

Lehmann U, Dieleman M, Martineau T. Staffing remote rural areas in middle- and low-income countries: a literature review of attraction and retention. BMC Health Serv Res 2008;8:19.

Lertkanokkun S, Okanurak K, Kaewkungwal J, Meksawasdichai N. Healthcare providers' knowledge, attitudes & practices regarding tuberculosis care. JITMM2012 Proceedings 2013;2:1-10.

Leung CC, Yew WW, Chan CK, Chang KC, Law WS, Lee SN, et al. Smoking adversely affects treatment response, outcome and relapse in tuberculosis. Eur Respir J 2015;45(3):738-45.

Levy MZ, Medeiros EA, Shang N, Soares MC, Homenko AS, Almeida RM, et al. TST reversion in a BCG-revaccinated population of nursing and medical students, Sao Paulo, Brazil, 1997-2000. Int J Tuberc Lung Dis 2005;9(7):771-6.

Lien LT, Hang NT, Kobayashi N, Yanai H, Toyota E, Sakurada S, et al. Prevalence and risk factors for tuberculosis infection among hospital workers in Hanoi, Vietnam. PLoS One 2009;4(8):e6798.

Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med 2007;4(1):e20.

Lin X, Chongsuvivatwong V, Lin L, Geater A, Lijuan R. Dose-response relationship between treatment delay of smear-positive tuberculosis patients and intra-household transmission: a cross-sectional study. Trans R Soc Trop Med Hyg 2008;102(8):797-804.

Liu Q, Liu L, Vu H, Liu X, Tang S, Wang H. Comparison between peer-led and teacher-led education in tuberculosis prevention in rural middle schools in Chongqing, China. Asia Pac J Public Health 2015;27(2):NP2101-11.

LoBue PA, Catanzaro A. Effectiveness of a nosocomial tuberculosis control program at an urban teaching hospital. Chest 1998;113(5):1184-9.

Locoh-Donou S, Guofen Y, Welcher M, Berry T, O'Connor RE, Brady WJ. Mass-gathering medicine: a descriptive analysis of a range of mass-gathering event types. Am J Emerg Med 2013;31(5):843-6.

Loddenkemper R, Bronnecke M, Castell S, Diel R. [Tuberculosis and Tobacco Smoking]. Pneumologie 2016;70(1):17-22.

Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis–a systematic review. BMC public health 2008;8(1):289.

Lopez AL, Aldaba JG, Ama CG, Sylim PG, Geraldino XD, Sarol JN, et al. Surveillance for tuberculosis in a rural community in The Philippines. Int J Tuberc Lung Dis 2016;20(11):1495-500.

Louther J, Rivera P, Feldman J, Villa N, DeHovitz J, Sepkowitz KA. Risk of tuberculin conversion according to occupation among health care workers at a New York City hospital. Am J Respir Crit Care Med 1997;156(1):201-5.

Luca S, Mihaescu T. History of BCG vaccine. Maedica (Buchar) 2013;8(1):53-8.

Lyon SM, Rossman MD. Pulmonary Tuberculosis. Microbiol Spectr 2017;5(1).

Ma X, Liu F, Liu L, Zhang L, Lu M, Abudukadeer A, et al. No MERS-CoV but positive influenza viruses in returning Hajj pilgrims, China, 2013-2015. BMC Infect Dis 2017;17(1):715.

Maciel EL, Viana MC, Zeitoune RC, Ferreira I, Fregona G, Dietze R. Prevalence and incidence of *Mycobacterium tuberculosis* infection in nursing students in Vitoria, Espirito Santo. Revista da Sociedade Brasileira de Medicina Tropical 2005;38(6):469-72.

REFERENCES

Mack U, Migliori GB, Sester M, Rieder HL, Ehlers S, Goletti D, et al. LTBI: latent tuberculosis infection or lasting immune responses to *M. tuberculosis*? A TBNET consensus statement. Eur Respir J 2009;33(5):956-73.

Madani TA, Ghabrah TM, Al-Hedaithy MA, Alhazmi MA, Alazraqi TA, Albarrak AM, et al. Causes of hospitalization of pilgrims in the Hajj season of the Islamic year 1423 (2003). Ann Saudi Med 2006;26(5):346-51.

Mahato RK, Laohasiriwong W, Vaeteewootacharn K, Koju R, Bhattarai R. Major Delays in the Diagnosis and Management of Tuberculosis Patients in Nepal. J Clin Diagn Res 2015;9(10):LC05-9.

Mahishale V, Patil B, Lolly M, Eti A, Khan S. Prevalence of Smoking and Its Impact on Treatment Outcomes in Newly Diagnosed Pulmonary Tuberculosis Patients: A Hospital-Based Prospective Study. Chonnam Med J 2015;51(2):86-90.

Makela V, Ala-Kulju K, Holst J, Siljander T. Tuberculosis--diagnosed and undiagnosed--as a cause of death. Autopsy observations. Scand J Respir Dis 1971;52(1):13-8.

Malangu N, Adebanjo OD. Knowledge and practices about multidrug-resistant tuberculosis amongst healthcare workers in Maseru. Afr J Prim Health Care Fam Med 2015;7(1).

Malangu N, Legothoane A. Analysis of occupational infections among health care workers in Limpopo province of South Africa. Glob J Health Sci 2012;5(1):44-51.

Mandourah Y, Al-Radi A, Ocheltree AH, Ocheltree SR, Fowler RA. Clinical and temporal patterns of severe pneumonia causing critical illness during Hajj. BMC Infect Dis 2012;12:117.

Manusov EG, Bradshaw RD, Fogarty JP. Tuberculosis screening in medical students. Fam Med 1996;28(9):645-9.

Marahatta SB. Multi-drug resistant tuberculosis burden and risk factors: an update. Kathmandu Univ Med J (KUMJ) 2010;8(29):116-25.

Marais BJ, Lonnroth K, Lawn SD, Migliori GB, Mwaba P, Glaziou P, et al. Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. Lancet Infect Dis 2013;13(5):436-48.

Marcus AM, Rose DN, Sacks HS, Schechter CB. BCG vaccination to prevent tuberculosis in health care workers: a decision analysis. Prev Med 1997;26(2):201-7.

Mase SR, Ramsay A, Ng V, Henry M, Hopewell PC, Cunningham J, et al. Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: a systematic review [Review Article]. The International Journal of Tuberculosis and Lung Disease 2007;11(5):485-95.

Masjedi MR, Hosseini M, Aryanpur M, Mortaz E, Tabarsi P, Soori H, et al. The effects of smoking on treatment outcome in patients newly diagnosed with pulmonary tuberculosis. Int J Tuberc Lung Dis 2017;21(3):351-6.

Matebesi Z, Timmerman C. The TB patient: Qualitative evidence of perceived factors affecting treatment compliance.

McCarthy KM, Scott LE, Gous N, Tellie M, Venter WD, Stevens WS, et al. High incidence of latent tuberculous infection among South African health workers: an urgent call for action. Int J Tuberc Lung Dis 2015;19(6):647-53.

Medrano BA, Salinas G, Sanchez C, Miramontes R, Restrepo BI, Haddad MB, et al. A missed tuberculosis diagnosis resulting in hospital transmission. Infect Control Hosp Epidemiol 2014;35(5):534-7.

Memish ZA. Hajj and the public health significance of mass gatherings. East Mediterr Health J 2013;19 Suppl 2:S5-6.

REFERENCES

Memish ZA, Al-Rabeeah AA. Public health management of mass gatherings: the Saudi Arabian experience with MERS-CoV . Bull World Health Organ 2013;91(12):899-A.

Memish ZA, Assiri A, Almasri M, Alhakeem RF, Turkestani A, Al Rabeeah AA, et al. Prevalence of MERS-CoV nasal carriage and compliance with the Saudi health recommendations among pilgrims attending the 2013 Hajj. J Infect Dis 2014.

Memish ZA, Assiri A, Turkestani A, Yezli S, Al Masri M, Charrel R, et al. Mass gathering and globalization of respiratory pathogens during the 2013 Hajj. Clin Microbiol Infect 2015a;21(6):571 e1-8.

Memish ZA, Filemban SM, Bamgboyel A, Al Hakeem RF, Elrashied SM, Al-Tawfiq JA. Knowledge and Attitudes of Doctors Toward People Living With HIV/AIDS in Saudi Arabia. Journal of acquired immune deficiency syndromes (1999) 2015b;69(1):61-7.

Mendes MA, Gaio R, Reis R, Duarte R. Contact screening in tuberculosis: can we identify those with higher risk? Eur Respir J 2013;41(3):758-60.

Mensah GI, Sowah SA, Yeboah NY, Addo KK, Jackson-Sillah D. Utility of QuantiFERON tuberculosis gold-in-tube test for detecting latent tuberculosis infection among close household contacts of confirmed tuberculosis patients in Accra, Ghana. Int J Mycobacteriol 2017;6(1):27-33.

Menzies D, Benedetti A, Paydar A, Martin I, Royce S, Pai M, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med 2009;6(9):e1000146.

Menzies D, Benedetti A, Paydar A, Royce S, Pai M, Burman W, et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. PLoS Medicine 2009;6(9):e1000150.

Menzies D, Fanning A, Yuan L, FitzGerald JM. Tuberculosis in health care workers: a multicentre Canadian prevalence survey: preliminary results. Canadian Collaborative Group in Nosocomial Transmission of Tuberculosis. Int J Tuberc Lung Dis 1998;2(9 Suppl 1):S98-102.

Menzies D, Fanning A, Yuan L, FitzGerald JM. Hospital ventilation and risk for tuberculous infection in canadian health care workers. Canadian Collaborative Group in Nosocomial Transmission of TB. Ann Intern Med 2000;133(10):779-89.

Menzies D, Fanning A, Yuan L, Fitzgerald M. Tuberculosis among health care workers. N Engl J Med 1995;332(2):92-8.

Menzies D, Joshi R, Pai M. Risk of tuberculosis infection and disease associated with work in health care settings. Int J Tuberc Lung Dis 2007;11(6):593-605.

Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. New England Journal of Medicine 2014;371(17):1588-98.

Mfinanga SG, Kirenga BJ, Chanda DM, Mutayoba B, Mthiyane T, Yimer G, et al. Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. The Lancet infectious diseases 2014;14(7):563-71.

Mikol EX, Horton R, Lincoln NS, Stokes AM. Incidence of pulmonary tuberculosis among employees of tuberculosis hospitals. Am Rev Tuberc 1952;66(1):16-27.

Miller AC, Polgreen LA, Cavanaugh JE, Hornick DB, Polgreen PM. Missed Opportunities to Diagnose Tuberculosis Are Common Among Hospitalized Patients and Patients Seen in Emergency Departments. Open Forum Infect Dis 2015;2(4):ofv171.

REFERENCES

Miller AK, Tepper A, Sieber K. Historical risks of tuberculin skin test conversion among non-physician staff at a large urban hospital. American Journal of Industrial Medicine 2002;42(3):228-35.

Minnery M, Contreras C, Perez R, Solorzano N, Tintaya K, Jimenez J, et al. A cross sectional study of knowledge and attitudes towards tuberculosis amongst front-line tuberculosis personnel in high burden areas of Lima, Peru. PLoS One 2013;8(9):e75698.

Mirsaeidi M, Sadikot RT. Patients at high risk of tuberculosis recurrence. Int J Mycobacteriol 2018;7(1):1-6.

Mirtskhulava V, Kempker R, Shields KL, Leonard MK, Tsertsvadze T, del Rio C, et al. Prevalence and risk factors for latent tuberculosis infection among health care workers in Georgia. Int J Tuberc Lung Dis 2008;12(5):513-9.

Mntonintshi M, O'Mahony D, Mabunda S, Namugenyi KAF. Undiagnosed tuberculosis in patients with HIV infection who present with severe anaemia at a district hospital. Afr J Prim Health Care Fam Med 2017;9(1):e1-e6.

Mnyambwa NP, Ngadaya ES, Kimaro G, Kim DJ, Kazwala R, Petrucka P, et al. Assessment of sputum smear-positive but culture-negative results among newly diagnosed pulmonary tuberculosis patients in Tanzania. Int J Gen Med 2017;10:199-205.

Moattari A, Emami A, Moghadami M, Honarvar B. Influenza viral infections among the Iranian Hajj pilgrims returning to Shiraz, Fars province, Iran. Influenza Other Respir Viruses 2012;6(6):e77-9.

Moh R, Badje A, N'Takpe J B, Kouame GM, Gabillard D, Ouassa T, et al. Screening for active tuberculosis before isoniazid preventive therapy among HIV-infected West African adults. Int J Tuberc Lung Dis 2017;21(12):1237-44.

Molina-Gamboa J, Fivera-Morales I, Ponce-de-Leon-Rosales S. Prevalence of tuberculin reactivity among healthcare workers from a Mexican hospital. Infect Control Hosp Epidemiol 1994;15(5):319-20.

Moodley P, Shah NS, Tayob N, Connolly C, Zetola N, Gandhi N, et al. Spread of extensively drug-resistant tuberculosis in KwaZulu-Natal province, South Africa. PLoS One 2011;6(5):e17513.

Moon HW, Kim H, Hur M, Yun YM, Lee A. Latent tuberculosis infection screening for laboratory personnel using interferon-gamma release assay and tuberculin skin test in Korea: an intermediate incidence setting. J Clin Lab Anal 2011;25(6):382-8.

Moro ML, Errante I, Infuso A, Sodano L, Gori A, Orcese CA, et al. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy. Int J Tuberc Lung Dis 2000;4(1):61-8.

Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infect Dis 2008;8(6):359-68.

Muntingh L. Race, gender and socioeconomic status in law enforcement in South Africa – are there worrying signs? 2013.

Mwandumba HC, Squire SB. Fully intermittent dosing with drugs for treating tuberculosis in adults. Cochrane Database Syst Rev 2001(4):Cd000970.

Myers JA. The prevention of tuberculosis among nurses. Am J Nurs 1930;30:1361-72.

Naidoo K, Yende-Zuma N, Padayatchi N, Naidoo K, Jithoo N, Nair G, et al. The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: findings from the SAPiT trial. Annals of internal medicine 2012;157(5):313-24.

REFERENCES

Naidoo S, Jinabhai CC. TB in health care workers in KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis 2006;10(6):676-82.

Naidoo S, Mahommed A. Knowledge, attitudes, behaviour and prevalence of TB infection among dentists in the western Cape. SADJ : journal of the South African Dental Association = tydskrif van die Suid-Afrikaanse Tandheelkundige Vereniging 2002;57(11):476-8.

Naidoo S, Taylor M, Esterhuizen TM, Nordstrom DL, Mohamed O, Knight SE, et al. Changes in healthcare workers' knowledge about tuberculosis following a tuberculosis training programme. Educ Health (Abingdon) 2011;24(2):514.

Nanoo A, Izu A, Ismail NA, Ihekweazu C, Abubakar I, Mametja D, et al. Nationwide and regional incidence of microbiologically confirmed pulmonary tuberculosis in South Africa, 2004-12: a time series analysis. Lancet Infect Dis 2015;15(9):1066-76.

Nardell EA, Sepkowitz KA. Tuberculosis transmission and control in hospitals and other institutions. In: Rom WN, Garay SM, editors. Tuberculosis. Philadelphia: Lippincott Williams & Wilkins; 2004.

Nasreen S, Shokoohi M, Malvankar-Mehta MS. Prevalence of Latent Tuberculosis among Health Care Workers in High Burden Countries: A Systematic Review and Meta-Analysis. PLoS One 2016;11(10):e0164034.

National Tuberculosis Controllers A, Centers for Disease C, Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR Recomm Rep 2005;54(RR-15):1-47.

Needham DM, Foster SD, Tomlinson G, Godfrey-Faussett P. Socio-economic, gender and health services factors affecting diagnostic delay for tuberculosis patients in urban Zambia. Trop Med Int Health 2001;6(4):256-9.

Nettleman MD, Fredrickson M, Good NL, Hunter SA. Tuberculosis control strategies: the cost of particulate respirators. Ann Intern Med 1994;121(1):37-40.

Nicol MP, Whitelaw A, Wendy S. Using Xpert MTB/RIF. Current Respiratory Medicine Reviews 2013;9:187-92.

Niemann S, Richter E, Rüsch-Gerdes S. Differentiation among Members of the Mycobacterium tuberculosis Complex by Molecular and Biochemical Features: Evidence for Two Pyrazinamide-Susceptible Subtypes ofM. bovis. Journal of clinical microbiology 2000;38(1):152-7.

Nienhaus A. Tuberculosis in healthcare workers. Pneumologie 2009;63(1):23-30.

Nienhaus A, Schablon A, Bacle CL, Siano B, Diel R. Evaluation of the interferon-gamma release assay in healthcare workers. Int Arch Occup Environ Health 2008;81(3):295-300.

Noe A, Ribeiro RM, Anselmo R, Maixenchs M, Sitole L, Munguambe K, et al. Knowledge, attitudes and practices regarding tuberculosis care among health workers in Southern Mozambique. BMC Pulm Med 2017;17(1):2.

Nunn AJ, Rusen I, Van Deun A, Torrea G, Phillips PP, Chiang C-Y, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials 2014;15(1):353.

Nyblade L, Stangl A, Weiss E, Ashburn K. Combating HIV stigma in health care settings: what works? J Int AIDS Soc 2009;12:15.

O'Donnell MR, Jarand J, Loveday M, Padayatchi N, Zelnick J, Werner L, et al. High incidence of hospital admissions with multidrug-resistant and extensively drug-resistant tuberculosis among South African health care workers. Ann Intern Med 2010;153(8):516-22.

REFERENCES

O'Grady J, Bates M, Chilukutu L, Mzyece J, Cheelo B, Chilufya M, et al. Evaluation of the Xpert MTB/RIF assay at a tertiary care referral hospital in a setting where tuberculosis and HIV infection are highly endemic. Clin Infect Dis 2012;55(9):1171-8.

O'Grady J, Maeurer M, Mwaba P, Kapata N, Bates M, Hoelscher M, et al. New and improved diagnostics for detection of drug-resistant pulmonary tuberculosis. Curr Opin Pulm Med 2011;17(3):134-41.

Ogbonnaya LU, Chukwu JN, Uwakwe KA, Oyibo PG, Ndukwe CD. The status of tuberculosis infection control measures in health care facilities rendering joint TB/HIV services in "German Leprosy and Tuberculosis Relief Association" supported states in Nigeria. Niger J Clin Pract 2011;14(3):270-5.

Okeyo ILA, Dowse R. An illustrated booklet for reinforcing community health worker knowledge of tuberculosis and facilitating patient counselling. Afr J Prim Health Care Fam Med 2018;10(1):e1-e7.

Olayemi SO, Oreagba IA, Akinyede A, Adepoju GE. Educational intervention and the health seeking attitude and adherence to therapy by tuberculosis patients from an urban slum in lagos Nigeria. Niger Postgrad Med J 2009;16(4):231-5.

Onozaki I, Law I, Sismanidis C, Zignol M, Glaziou P, Floyd K. National tuberculosis prevalence surveys in Asia, 1990-2012: an overview of results and lessons learned. Trop Med Int Health 2015;20(9):1128-45.

Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. The Lancet infectious diseases 2009;9(3):153-61.

Organization WH, Organization WH. Use of liquid TB culture and drug susceptibility testing (DST) in low and medium income settings. Geneva: World Health Organization 2007.

Organization. WH. The use of liquid medium for culture and DST. World Health Organization, Geneva, Switzerland http://www who int/tb/dots/laboratory/policy/en/index3 html 2007.

Orrett FA. Prevalence of tuberculin skin test reactivity among health care workers at a teaching hospital in Trinidad. Clin Microbiol Infect 2000;6(1):45-8.

Ozdemir D, Annakkaya AN, Tarhan G, Sencan I, Cesur S, Balbay O, et al. Comparison of the tuberculin skin test and the quantiferon test for latent *Mycobacterium tuberculosis* infections in health care workers in Turkey. Jpn J Infect Dis 2007;60(2-3):102-5.

Pablos-Mendez A, Sterling TR, Frieden TR. The relationship between delayed or incomplete treatment and all-cause mortality in patients with tuberculosis. JAMA 1996;276(15):1223-8.

Padmapriyadarsini C, Bhavani PK, Sekar L, Anandhachitra, Selvaraj M, Poornagangadevi N, et al. Effectiveness of symptom screening and incidence of tuberculosis among adults and children living with HIV infection in India. Natl Med J India 2016;29(6):321-5.

Pai M, Dendukuri N, Wang L, Joshi R, Kalantri S, Rieder HL. Improving the estimation of tuberculosis infection prevalence using T-cell-based assay and mixture models. Int J Tuberc Lung Dis 2008;12(8):895-902.

Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. Clin Microbiol Rev 2014;27(1):3-20.

Pai M, Gokhale K, Joshi R, Dogra S, Kalantri S, Mendiratta DK, et al. Mycobacterium tuberculosis infection in health care workers in rural India: comparison of a whole-blood interferon gamma assay with tuberculin skin testing. Jama 2005;293(22):2746-55.

REFERENCES

Pakenham-Walsh N, Bukachi F. Information needs of health care workers in developing countries: a literature review with a focus on Africa. Hum Resour Health 2009;7:30.

Pan SC, Chen YC, Wang JY, Sheng WH, Lin HH, Fang CT, et al. Tuberculosis in healthcare workers: A matched cohort study in Taiwan. PLoS One 2015a;10(12):e0145047.

Pan SC, Ku CC, Kao D, Ezzati M, Fang CT, Lin HH. Effect of diabetes on tuberculosis control in 13 countries with high tuberculosis: a modelling study. Lancet Diabetes Endocrinol 2015b;3(5):323-30.

Parsons LM, Brosch R, Cole ST, Somoskövi Á, Loder A, Bretzel G, et al. Rapid and simple approach for identification of Mycobacterium tuberculosis complex isolates by PCR-based genomic deletion analysis. Journal of clinical microbiology 2002;40(7):2339-45.

Peltzer K. Tuberculosis non-communicable disease comorbidity and multimorbidity in public primary care patients in South Africa. Afr J Prim Health Care Fam Med 2018;10(1):e1-e6.

Piatek AS, Van Cleeff M, Alexander H, Coggin WL, Rehr M, Van Kampen S, et al. GeneXpert for TB diagnosis: planned and purposeful implementation. Glob Health Sci Pract 2013;1(1):18-23.

Piubello A, Harouna SH, Souleymane M, Boukary I, Morou S, Daouda M, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. The International Journal of Tuberculosis and Lung Disease 2014;18(10):1188-94.

Plitt SS, Soskolne CL, Fanning EA, Newman SC. Prevalence and determinants of tuberculin reactivity among physicians in Edmonton, Canada: 1996-1997. Int J Epidemiol 2001;30(5):1022-8.

Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respiratory Soc; 2016.

Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2016;4:Cd002244.

Puchalski Ritchie LM, van Lettow M, Barnsley J, Chan AK, Schull MJ, Martiniuk AL, et al. Lay Health Workers experience of a tailored knowledge translation intervention to improve job skills and knowledge: a qualitative study in Zomba district Malawi. BMC Med Educ 2016;16:54.

Qadeer E, Fatima R, Yaqoob A, Tahseen S, Ul Haq M, Ghafoor A, et al. Population Based National Tuberculosis Prevalence Survey among Adults (>15 Years) in Pakistan, 2010-2011. PLoS One 2016;11(2):e0148293.

Querri A, Ohkado A, Yoshimatsu S, Coprada L, Lopez E, Medina A, et al. Enhancing tuberculosis patient detection and care through community volunteers in the urban poor, The Philippines. Public Health Action 2017;7(4):268-74.

Rabaan AA. Middle East respiratory syndrome coronavirus: five years later. Expert Rev Respir Med 2017;11(11):901-12.

Rabahi MF, Junqueira-Kipnis AP, Dos Reis MC, Oelemann W, Conde MB. Humoral response to HspX and GlcB to previous and recent infection by *Mycobacterium tuberculosis*. BMC Infect Dis 2007;7:148.

Rafiza S, Rampal KG, Tahir A. Prevalence and risk factors of latent tuberculosis infection among health care workers in Malaysia. BMC Infect Dis 2011;11:19.

Rajagopalan S. Tuberculosis and aging: a global health problem. Clin Infect Dis 2001;33(7):1034-9.

Ramirez JA, Anderson P, Herp S, Raff MJ. Increased rate of tuberculin skin test conversion among workers at a university hospital. Infect Control Hosp Epidemiol 1992;13(10):579-81.

REFERENCES

Rao KG, Aggarwal AN, Behera D. Tuberculosis among physicians in training. Int J Tuberc Lung Dis 2004;8(11):1392-4.

Rao VG, Bhat J, Yadav R, Gopalan GP, Nagamiah S, Bhondeley MK, et al. Prevalence of pulmonary tuberculosis--a baseline survey in central India. PLoS One 2012;7(8):e43225.

Rees D, Murray J. Silica, silicosis and tuberculosis. Int J Tuberc Lung Dis 2007;11(5):474-84.

Reyes-Guillen I, Sanchez-Perez HJ, Cruz-Burguete J, Izaurieta-de Juan M. Anti-tuberculosis treatment defaulting: an analysis of perceptions and interactions in Chiapas, Mexico. Salud Publica Mex 2008;50(3):251-7.

Rieder HL. Epidemiologic basis of tuberculosis control: International Union Against Tuberculosis and Lung Disease (IUATLD), 1999.

Rieder HL, Chiang C, Rusen I. A method to determine the utility of the third diagnostic and the second follow-up sputum smear examinations to diagnose tuberculosis cases and failures. The International Journal of Tuberculosis and Lung Disease 2005;9(4):384-91.

Roberts FJ, Trueman MR, Trueman GE. Undiagnosed tuberculosis at autopsy. Can J Public Health 1971;62(6):496-502.

Rodriguez Bayarri MJ, Madrid San Martin F. Pulmonary tuberculosis as an occupational disease. Arch Bronconeumol 2004;40(10):463-72.

Rogerio WP, Baraona CM, do Prado TN, Lacerda TC, Carlesso GF, Maciel EL. [Prevalence of latent infection of mycobacterium tuberculosis among healthcare students in a public university in Vitoria, state of Espirito Santo, Brazil]. Cien Saude Colet 2013;18(5):1331-9.

Rose HG. Tuberculosis in medical students. N Engl J Med 1953:248:956.

Rosenthal T, Pitlik S, Michaeli D. Fatal undiagnosed tuberculosis in hospitalized patients. J Infect Dis 1975;131 Suppl:S51-6.

Rossato Silva D, Muller AM, Dalcin Pde T. Factors associated with delayed diagnosis of tuberculosis in hospitalized patients in a high TB and HIV burden setting: a cross-sectional study. BMC Infect Dis 2012;12:57.

Roth VR, Garrett DO, Laserson KF, Starling CE, Kritski AL, Medeiros EA, et al. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals. Int J Tuberc Lung Dis 2005;9(12):1335-42.

Rullan JV, Herrera D, Cano R, Moreno V, Godoy P, Peiro EF, et al. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* in Spain. Emerg Infect Dis 1996;2(2):125-9.

Sanchez-Barriga JJ. Mortality trends and risk of dying from pulmonary tuberculosis in the 7 socioeconomic regions and the 32 States of Mexico, 2000-2009. Arch Bronconeumol 2015;51(1):16-23.

Santha T, Garg R, Subramani R, Chandrasekaran V, Selvakumar N, Sisodia R, et al. Comparison of cough of 2 and 3 weeks to improve detection of smear-positive tuberculosis cases among out-patients in India. The International Journal of Tuberculosis and Lung Disease 2005;9(1):61-8.

Saqib MA, Awan IN, Rizvi SK, Shahzad MI, Mirza ZS, Tahseen S, et al. Delay in diagnosis of tuberculosis in Rawalpindi, Pakistan. BMC Res Notes 2011;4:165.

Saqib SE, Ahmad MM, Amezcua-Prieto C, Martinez-Ruiz V. Treatment Delay among Pulmonary Tuberculosis Patients within the Pakistan National Tuberculosis Control Program. Am J Trop Med Hyg 2018;99(1):143-9.

Saudi Ministry of Health. Basics of Tuberculosis Control in Saudi Arabia. In: Public Health Agency NTCP, Ministry of Health, Kingdom of Saudi Arabia, editor. 2014.

REFERENCES

Schmidt BM, Engel ME, Abdullahi L, Ehrlich R. Effectiveness of control measures to prevent occupational tuberculosis infection in health care workers: a systematic review. BMC Public Health 2018;18(1):661.

Seidler A, Nienhaus A, Diel R. Review of epidemiological studies on the occupational risk of tuberculosis in low-incidence areas. Respiration 2005;72(4):431-46.

Senkoro M, Mfinanga S, Egwaga S, Mtandu R, Kamara DV, Basra D, et al. Prevalence of pulmonary tuberculosis in adult population of Tanzania: a national survey, 2012. Int J Tuberc Lung Dis 2016;20(8):1014-21.

Sepkowitz KA. Tuberculosis and the health care worker: a historical perspective. Ann Intern Med 1994;120(1):71-9.

Seung KJ, Keshavjee S, Rich ML. Multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. Cold Spring Harb Perspect Med 2015;5(9):a017863.

Severo KG, Oliveira Jda S, Carneiro M, Valim AR, Krummenauer EC, Possuelo LG. Latent tuberculosis in nursing professionals of a Brazilian hospital. J Occup Med Toxicol 2011;6(1):15.

Shirah BH, Zafar SH, Alferaidi OA, Sabir AMM. Mass gathering medicine (Hajj pilgrimage in Saudi Arabia): The clinical pattern of pneumonia among pilgrims during Hajj. J Infect Public Health 2017;10(3):277-86.

Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Zungu N, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town, HSRC Press.2014.

Shrestha A, Bhattarai D, Thapa B, Basel P, Wagle RR. Health care workers' knowledge, attitudes and practices on tuberculosis infection control, Nepal. BMC Infect Dis 2017;17(1):724.

Shuaib YA, Khalil EAG, Schaible UE, Wieler LH, Bakheit MAM, Mohamed-Noor SE, et al. Smear Microscopy for Diagnosis of Pulmonary Tuberculosis in Eastern Sudan. Tuberc Res Treat 2018;2018:8038137.

Silva DR, Munoz-Torrico M, Duarte R, Galvao T, Bonini EH, Arbex FF, et al. Risk factors for tuberculosis: diabetes, smoking, alcohol use, and the use of other drugs. J Bras Pneumol 2018;44(2):145-52.

Silva VM, Cunha AJ, Kritski AL. Tuberculin skin test conversion among medical students at a teaching hospital in Rio de Janeiro, Brazil. Infect Control Hosp Epidemiol 2002;23(10):591-4.

Singla N, Sharma PP, Singla R, Jain RC. Survey of knowledge, attitudes and practices for tuberculosis among general practitioners in Delhi, India. Int J Tuberc Lung Dis 1998;2(5):384-9.

Skodric V, Savic B, Jovanovic M, Pesic I, Videnovic J, Zugic V, et al. Occupational risk of tuberculosis among health care workers at the Institute for Pulmonary Diseases of Serbia. Int J Tuberc Lung Dis 2000;4(9):827-31.

Slama K, Chiang C, Enarson D, Hassmiller K, Fanning A, Gupta P, et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. The International Journal of Tuberculosis and Lung Disease 2007;11(10):1049-61.

Smetana GW, Landon BE, Bindman AB, Burstin H, Davis RB, Tjia J, et al. A comparison of outcomes resulting from generalist vs specialist care for a single discrete medical condition: a systematic review and methodologic critique. Arch Intern Med 2007;167(1):10-20.

Smith-Palmer A, Oates K, Webster D, Taylor S, Scott KJ, Smith G, et al. Outbreak of *Neisseria meningitidis* capsular group W among scouts returning from the World Scout Jamboree, Japan, 2015. Euro Surveill 2016;21(45).

Snider DE. Tuberculosis. In: Weeks JL, Levy BS, Wagner GR, editors. Preventing Occupational Disease and Injury. Washington, DC: American Health Association; 1991.

REFERENCES

Soborg B, Andersen AB, Larsen HK, Weldingh K, Andersen P, Kofoed K, et al. Detecting a low prevalence of latent tuberculosis among health care workers in Denmark detected by M. tuberculosis specific IFN-gamma whole-blood test. Scand J Infect Dis 2007;39(6-7):554-9.

Somily AM, Barry MA, Habib HA, Alotaibi FE, Al-Zamil FA, Khan MA, et al. Evaluation of GeneXpert MTB/RIF for detection of Mycobacterium tuberculosis complex and rpo B gene in respiratory and non-respiratory clinical specimens at a tertiary care teaching hospital in Saudi Arabia. Saudi Med J 2016;37(12):1404-7.

Spindola De Miranda S, Campos De Oliveira A, Xavier Santos A, Pereira Prado D, Leao Soares C, Santos Nery R, et al. Positive tuberculin test and risk of infection by *Mycobacterium tuberculosis* in a tuberculosis clinic settled in an upright building, in Minas Gerais, Brazil. Revista medica de Chile 2012;140(8):1022-7.

Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. BMC Infect Dis 2009;9:91.

Sridhar S, Karnani N, Connell DW, Millington KA, Dosanjh D, Bakir M, et al. Increased risk of Mycobacterium tuberculosis infection in household child contacts exposed to passive tobacco smoke. Pediatr Infect Dis J 2014;33(12):1303-6.

Sridhar S, Regner I, Brouqui P, Gautret P. Methodologies for measuring travelers' risk perception of infectious diseases: A systematic review. Travel Med Infect Dis 2016;14(4):360-72.

Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. The Lancet infectious diseases 2006;6(9):570-81.

Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M, et al. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev 2013(1):Cd009593.

Stevenson CR, Critchley JA, Forouhi NG, Roglic G, Williams BG, Dye C, et al. Diabetes and the risk of tuberculosis: a neglected threat to public health? Chronic illness 2007;3(3):228-45.

Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health 2008;8:15.

Stuart RL, Bennett NJ, Forbes AB, Grayson ML. Assessing the risk of tuberculosis infection among healthcare workers: the Melbourne Mantoux Study. Melbourne Mantoux Study Group. Med J Aust 2001;174(11):569-73.

Talebi-Taher M, Javad-Moosavi SA, Entezari AH, Shekarabi M, Parhizkar B. Comparing the performance of QuantiFERON-TB Gold and Mantoux test in detecting latent tuberculosis infection among Iranian health care workers. International journal of occupational medicine and environmental health 2011;24(4):359-66.

Tam CM, Leung CC. Occupational tuberculosis: a review of the litherature and the local situation. Hong Kong Med J 2006;12:448-55.

Teixeira EG, Kritski A, Ruffino-Netto A, Steffen R, Lapa e Silva JR, Belo M, et al. Medical students at risk of nosocomial tuberculosis. J Hosp Infect 2011;77(1):80-1.

Temesgen C. Knowledge and practice of tuberculosis infection control among health professionals in Bahir Dar, West and East Gojjam zone Hospital; Northwest Ethiopia. BMC Health Serv Res 2011;14:593.

Tenna A, Stenehjem EA, Margoles L, Kacha E, Blumberg HM, Kempker RR. Infection control knowledge, attitudes, and practices among healthcare workers in Addis Ababa, Ethiopia. Infect Control Hosp Epidemiol 2013;34(12):1289-96.

REFERENCES

The Lancet Diabetes E. Diabetes and tuberculosis--a wake-up call. Lancet Diabetes Endocrinol 2014;2(9):677.

Thwaites GE, Bang ND, Dung NH, Quy HT, Oanh DTT, Thoa NTC, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. New England Journal of Medicine 2004;351(17):1741-51.

Topic RZ, Dodig S, Zoricic-Letoja I. Interferon-gamma and immunoglobulins in latent tuberculosis infection. Arch Med Res 2009;40(2):103-8.

Torres Costa J, Silva R, Ringshausen FC, Nienhaus A. Screening for tuberculosis and prediction of disease in Portuguese healthcare workers. J Occup Med Toxicol 2011;6:19.

Trajman A, Steffen RE, Menzies D. Interferon-Gamma Release Assays versus Tuberculin Skin Testing for the diagnosis of latent tuberculosis infection: An overview of the evidence. Pulm Med 2013;2013:601737.

Tripodi D, Brunet-Courtois B, Nael V, Audrain M, Chailleux E, Germaud P, et al. Evaluation of the tuberculin skin test and the interferon-gamma release assay for TB screening in French healthcare workers. J Occup Med Toxicol 2009;4:30.

Tudor C, Van der Walt M, Margot B, Dorman SE, Pan WK, Yenokyan G, et al. Tuberculosis among health care workers in KwaZulu-Natal, South Africa: a retrospective cohort analysis. BMC Public Health 2014;14:891.

Uebel K, Friedland G, Pawinski R, Holst H. HAART for hospital health care workers--an innovative programme. S Afr Med J 2004;94(6):423-7.

Usui T, Yamanaka K, Nomura H, Tokudome S. Elevated risk of tuberculosis by occupation with special reference to health care workers. J Epidemiol 2000;10(1):1-6.

Uys L, Chirwa M, Kohi T, Greeff M, Naidoo J, Makoae L, et al. Evaluation of a health setting-based stigma intervention in five African countries. AIDS Patient Care STDS 2009;23(12):1059-66.

van der Werf MJ, Langendam MW, Huitric E, Manissero D. Knowledge of tuberculosis-treatment prescription of health workers: a systematic review. Eur Respir J 2012;39(5):1248-55.

Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. American journal of respiratory and critical care medicine 2010;182(5):684-92.

Van Rie A, Page-Shipp L, Scott L, Sanne I, Stevens W. Xpert((R)) MTB/RIF for point-of-care diagnosis of TB in high-HIV burden, resource-limited countries: hype or hope? Expert Rev Mol Diagn 2010;10(7):937-46.

Van't Hoog A, Langendam M, Mitchell E, Cobelens F, Sinclair D, Leeflang M, et al. A systematic review of the sensitivity and specificity of symptom-and chest-radiography screening for active pulmonary tuberculosis in HIV-negative persons and persons with unknown HIV status. REPORT-Version March 2013. World Health Organization, Geneva, Switzerland: WHO 2013.

Vandan N, Ali M, Prasad R, Kuroiwa C. Assessment of doctors' knowledge regarding tuberculosis management in Lucknow, India: a public-private sector comparison. Public Health 2009;123(7):484-9.

Vanden Driessche K, Sabue M, Dufour W, Behets F, Van Rie A. Training health care workers to promote HIV services for patients with tuberculosis in the Democratic Republic of Congo. Hum Resour Health 2009;7:23.

Vinton P, Mihrshahi S, Johnson P, Jenkin GA, Jolley D, Biggs BA. Comparison of QuantiFERON-TB Gold In-Tube Test and tuberculin skin test for identification of latent *Mycobacterium*

tuberculosis infection in healthcare staff and association between positive test results and known risk factors for infection. Infect Control Hosp Epidemiol 2009;30(3):215-21.
von Delft A, Dramowski A, Khosa C, Kotze K, Lederer P, Mosidi T, et al. Why healthcare workers are sick of TB. Int J Infect Dis 2015;32:147-51.
von Delft A, Dramowski A, Sifumba Z, Mosidi T, Xun Ting T, von Delft D, et al. Exposed, but not protected: more is needed to prevent drug-resistant tuberculosis in healthcare workers and students. Clin Infect Dis 2016;62 Suppl 3:S275-80.
Wade VA, Karnon J, Eliott JA, Hiller JE. Home videophones improve direct observation in tuberculosis treatment: a mixed methods evaluation. PLoS one 2012;7(11):e50155.
Wahab FA, Abdullah S, Abdullah JM, Jaafar H, Noor SS, Mohammad WM, et al. Updates on Knowledge, Attitude and Preventive Practices on Tuberculosis among Healthcare Workers. Malays J Med Sci 2016;23(6):25-34.
Wajanga BM, Peck RN, Kalluvya S, Fitzgerald DW, Smart LR, Downs JA. Healthcare worker perceived barriers to early initiation of antiretroviral and tuberculosis therapy among Tanzanian inpatients. PLoS One 2014;9(2):e87584.
Wang L, Zhang H, Ruan Y, Chin DP, Xia Y, Cheng S, et al. Tuberculosis prevalence in China, 1990-2010; a longitudinal analysis of national survey data. Lancet 2014;383(9934):2057-64.
Warren DK, Foley KM, Polish LB, Seiler SM, Fraser VJ. Tuberculin skin testing of physicians at a midwestern teaching hospital: a 6-year prospective study. Clin Infect Dis 2001;32(9):1331-7.
Wei X, Zhang X, Yin J, Walley J, Beanland R, Zou G, et al. Changes in pulmonary tuberculosis prevalence: evidence from the 2010 population survey in a populous province of China. BMC Infect Dis 2014;14:21.
Wei Z, Yang M, Quan B, Wang Y, Wu Y, Ji B. Prevalence of latent tuberculosis infection among healthcare workers in China as detected by two interferon-gamma release assays. J Hosp Infect 2013;84(4):323-5.
Whitaker JA, Mirtskhulava V, Kipiani M, Harris DA, Tabagari N, Kempker RR, et al. Prevalence and incidence of latent tuberculosis infection in georgian healthcare workers. PLoS One 2013;8(3):e58202.
Whittington RM. Fatal but clinically undiagnosed tuberculosis. J R Coll Gen Pract 1983;33(251):343-5.
Wilder-Smith A, Foo W, Earnest A, Paton NI. High risk of *Mycobacterium tuberculosis* infection during the Hajj pilgrimage. Trop Med Int Health 2005;10(4):336-9.
Wilder-Smith A, Foo W, Earnest A, Paton NI. High risk of Mycobacterium tuberculosis infection during the Hajj pilgrimage. Tropical Medicine & International Health 2005;10(4):336-9.
Wilkinson D, Gilks CF. Increasing frequency of tuberculosis among staff in a South African district hospital: impact of the HIV epidemic on the supply side of health care. Trans R Soc Trop Med Hyg 1998;92(5):500-2.
Williams CT. The contagion of phthisis. Br Med J 1882:618-21.
Williams CT. Infection of consumption. Br Med J 1909;2(2538):433-7.
Wiysonge CS, Ntsekhe M, Thabane L, Volmink J, Majombozi D, Gumedze F, et al. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev 2017;9:Cd000526.
Woith W, Volchenkov G, Larson J. Barriers and motivators affecting tuberculosis infection control practices of Russian health care workers. Int J Tuberc Lung Dis 2012;16(8):1092-6.
Woith WM, Volchenkov G, Larson JL. Russian health care workers' knowledge of tuberculosis and infection control. Int J Tuberc Lung Dis 2010;14(11):1489-92.

REFERENCES

Wong EB, Omar T, Setlhako GJ, Osih R, Feldman C, Murdoch DM, et al. Causes of death on antiretroviral therapy: a post-mortem study from South Africa. PLoS One 2012;7(10):e47542.

Wood R, Middelkoop K, Myer L, Grant AD, Whitelaw A, Lawn SD, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. Am J Respir Crit Care Med 2007;175(1):87-93.

World Health Organization. Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings. Geneva1999.

World Health Organization. Training for better TB control. Geneva2002.

World Health Organization. Humanitarian Health Action: Afghanistan: Country profile. 2004.

World Health Organization. The global plan to stop TB 2006-2015. Geneva2006a.

World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: World Health Organization, 2006b.

World Health Organization. Strengthening the teaching of tuberculosis control in basic training programmes: A manual for instructors of nurses and other health care workers. Geneva2006c.

World Health Organization. Advocacy, communication and social mobilization for TB control: A guide to developing knowledge, attitude and practice surveys. Geneva, Switzerland2008a.

World Health Organization. Communicable disease alert and response for mass gatherings: Key considerations. Geneva, Switzerland2008b.

World Health Organization. Management of Tuberculosis Training for Health Facility Staff - 2nd edition. WHO/HTM/TB/2009. Geneva2009a.

World Health Organization. WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva2009b.

World Health Organization. Proposed reduction of number of smears for the diagnosis of pulmonary TB: Background document. World Health Organization2007Proposed reduction of number of smears for the diagnosis of pulmonary TB: background document Expert Group Meeting, Geneva Available: http://www who int/tb/dots/laboratory/Reduction% 20of% 20smears pdf Accessed2010a.

World Health Organization. Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB. Geneva, Switzerland.2010b.

World Health Organization. Treatment of tuberculosis guidelines- Fourth edition. Geneva, Switzerland2010c.

World Health Organization. Treatment of tuberculosis: guidelines. Geneva: World Health Organization; 2010d.

World Health Organization. Early detection of tuberculosis: an overview of approaches, guidelines and tools. 2011a.

World Health Organization. Fluorescent light-emitting diode (LED) microscopy for diagnosis of tuberculosis: policy statement. 2011b.

World Health Organization. Policy statement: automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement: automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system 2011c.

World Health Organization. Electronic recording and reporting for tuberculosis care and control. 2012.

World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MT. 2013a.

World Health Organization. Definitions and reporting framework for tuberculosis–2013 revision. 2013b.
World Health Organization. Systematic screening for active tuberculosis: principles and recommendations: World Health Organization, 2013c.
World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. 2014a.
World Health Organization. The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva2014b.
World Health Organization. Global tuberculosis report. Geneva, Switzerland2014c.
World Health Organization. Xpert MTB/RIF implementation manual. Technical and operational 'how-to': practical considerations. Geneva, Switzerland: WHO; 2014. WHO/HTM/TB/2014.1. http://apps. who. int/iris/bitstream/10665/112469/1/9789241506700_eng. pdf; 2014d.
World Health Organization. Gear up to end TB: introducing the end TB strategy. World Health Organization; 2015a.
World Health Organization. Global tuberculosis report 2015. Geneva2015b.
World Health Organization. Implementing tuberculosis diagnostics: policy framework. 2015c.
World Health Organization. Public Health for Mass Gatherings: Key Considerations. Geneva, Switzerland2015d.
World Health Organization. The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: policy guidance. 2015e.
World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach: World Health Organization, 2016a.
World Health Organization. The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis: policy guidance. 2016b.
World Health Organization. The use of molecular line probe assay for the detection of resistance to isoniazid and rifampicin: policy update. 2016c.
World Health Organization. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance. 2016d.
World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis 2016 update: World Health Organization, 2016e.
World Health Organization. Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis: World Health Organization, 2017a.
World Health Organization. Global tuberculosis report 2017. Geneva2017b.
World Health Organization. Guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update. 2017c.
World Health Organization. HIV-Associated Tuberculosis. Geneva, Switzerland2017d.
World Health Organization. Next-generation Xpert® MTB/RIF Ultra assay recommended by WHO. 2017e.
World Health Organization. WHO meeting report of a technical expert consultation: non-inferiority analysis of Xpert MT. 2017f.
World Health Organization. BCG vaccines: WHO position paper - February 2018. Wkly Epidemiol Rec 2018a;93(8):73-96.
World Health Organization. Global tuberculosis report 2018. Geneva, Switzerland2018b.

REFERENCES

World Health Organization. Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management. Geneva, Switzerland2018c.

World Health Organization. Technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. 2018d.

World Health Organization. WHO treatment guidelines for isoniazid-resistant tuberculosis: supplement to the WHO treatment guidelines for drug-resistant tuberculosis. 2018e.

Wu S, Roychowdhury I, Khan M. Evaluating the impact of healthcare provider training to improve tuberculosis management: a systematic review of methods and outcome indicators used. Int J Infect Dis 2017a;56:105-10.

Wu S, Roychowdhury I, Khan M. Evaluations of training programs to improve human resource capacity for HIV, malaria, and TB control: a systematic scoping review of methods applied and outcomes assessed. Trop Med Health 2017b;45:16.

Xiao S, Li Y, Sung M, Wei J, Yang Z. A study of the probable transmission routes of MERS-CoV during the first hospital outbreak in the Republic of Korea. Indoor Air 2018;28(1):51-63.

Yan S, Chen L, Wu W, Fu Z, Zhang H, Li Z, et al. Early versus Delayed Antiretroviral Therapy for HIV and Tuberculosis Co-Infected Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLOS ONE 2015;10(5):e0127645.

Yanai H, Limpakarnjanarat K, Uthaivoravit W, Mastro TD, Mori T, Tappero JW. Risk of *Mycobacterium tuberculosis* infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis 2003;7(1):36-45.

Yang WT, Gounder CR, Akande T, De Neve JW, McIntire KN, Chandrasekhar A, et al. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? Tuberc Res Treat 2014;2014:461935.

Yezli S, Alotaibi B. Mass gatherings and mass gatherings health. Saudi Med J 2016;37(7):729-30.

Yezli S, Assiri AM, Alhakeem RF, Turkistani AM, Alotaibi B. Meningococcal disease during the Hajj and Umrah mass gatherings. Int J Infect Dis 2016;47:60-4.

Yezli S, Memish ZA. Tuberculosis in Saudi Arabia: prevalence and antimicrobial resistance. Journal of Chemotherapy 2012;24(1):1-5.

Yezli S, Yassin Y, Awam A, Attar A, Al-Jahdali E, Alotaibi B. Umrah. An opportunity for mass gatherings health research. Saudi Med J 2017a;38(8):868-71.

Yezli S, Zumla A, Yassin Y, Al-Shangiti AM, Mohamed G, Turkistani AM, et al. Undiagnosed active pulmonary tuberculosis among pilgrims during the 2015 Hajj mass gathering: A prospective cross-sectional study. Am J Trop Med Hyg 2017b;97(5):1304-9.

Young F, Critchley JA, Johnstone LK, Unwin NC. A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization. Global Health 2009;5:9.

Yu CT, Zantua RRR, Sto T, Linus JH. Pulmonary tuberculosis: Knowledge, attitudes and practices of selected physicians in a tertiary-care hospital. Phil J Microbiol Infect Dis 2002;31(1):1-8.

Yuen CM, Amanullah F, Dharmadhikari A, Nardell EA, Seddon JA, Vasilyeva I, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. Lancet 2015;386(10010):2334-43.

Zahnow K, Matts JP, Hillman D, Finley E, Brown LS, Jr., Torres RA, et al. Rates of tuberculosis infection in healthcare workers providing services to HIV-infected populations. Terry Beirn Community Programs for Clinical Research on AIDS. Infect Control Hosp Epidemiol 1998;19(11):829-35.

REFERENCES

Zaman K, Hossain S, Banu S, Quaiyum MA, Barua PC, Salim MA, et al. Prevalence of smear-positive tuberculosis in persons aged >/= 15 years in Bangladesh: results from a national survey, 2007-2009. Epidemiol Infect 2012;140(6):1018-27.

Zaman K, Yunus M, Arifeen SE, Baqui AH, Sack DA, Hossain S, et al. Prevalence of sputum smear-positive tuberculosis in a rural area in Bangladesh. Epidemiol Infect 2006;134(5):1052-9.

Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and meta-analysis. PLoS One 2019;14(1):e0210422.

Zhang LF, Liu XQ, Zhang Y, Deng GH, Pareek M, Lalvani A. A prospective longitudinal study evaluating a T-cell-based assay for latent tuberculosis infection in health-care workers in a general hospital in Beijing. Chinese medical journal 2013;126(11):2039-44.

Zhao M, Li X, Xu P, Shen X, Gui X, Wang L, et al. Transmission of MDR and XDR tuberculosis in Shanghai, China. PLoS One 2009;4(2):e4370.

Zheng X, Zhong F, Zhang X. Doctors' compliance with national guidelines and clinical pathway on the treatment of tuberculosis inpatients in Hubei, China. Journal of evaluation in clinical practice 2014;20(3):288-93.

Zhou F, Zhang L, Gao L, Hao Y, Zhao X, Liu J, et al. Latent tuberculosis infection and occupational protection among health care workers in two types of public hospitals in China. PLoS One 2014;9(8):e104673.

Ziyaeyan M, Alborzi A, Jamalidoust M, Moeini M, Pouladfar GR, Pourabbas B, et al. Pandemic 2009 influenza A (H1N1) infection among 2009 Hajj Pilgrims from Southern Iran: a real-time RT-PCR-based study. Influenza Other Respir Viruses 2012;6(6):e80-4.

Zumla A, Davies PD. Progress towards achieving global tuberculosis control: so near, yet so far. Int J Tuberc Lung Dis 2016;20(3):285-6.

Zumla A, Saeed AB, Alotaibi B, Yezli S, Dar O, Bieh K, et al. Tuberculosis and mass gatherings—opportunities for defining burden, transmission risk, and the optimal surveillance, prevention, and control measures at the annual Hajj pilgrimage. International Journal of Infectious Diseases 2016;47:86-91.

Zwerling A, Cojocariu M, McIntosh F, Pietrangelo F, Behr MA, Schwartzman K, et al. TB screening in Canadian health care workers using interferon-gamma release assays. PLoS One 2012;7(8):e43014.

Appendix 1: Data collection form for non-hospitalised pilgrims symptomatic for cough

Verbal consent obtained (check √) ☐ **Name** ____________________ **Signature** ____________________

Section (1): Demographics Data

1.1.Passport page copy attached: ☐ Yes ☐ No

(If Yes, Please proceed to question 1.7)

1.2.Full Name: ____________________

1. 3.Gender: ☐ Male ☐ Female

1. 4.Date of birth: DD / MM / YYYY

OR Age (in years): ____________________

1.5. Nationality: ____________________

1.6. Passport / Iqama / ID No.: ____________________

1.7. What is the highest level of education you have achieved?

(Tick in appropriate boxes)

☐ University/Higher education ☐ Secondary education

☐ Primary education ☐ No formal education

1.8. Which of these best describes your job?

(Tick in appropriate boxes)

☐ Health care worker ☐ Laboratory personnel

☐ Refugee camp worker ☐ Prison staff

☐ Miner ☐ None of the above

Section (2): Health Conditions & Epidemiological Risk Factors

2.1. How long have you had this cough for? __________ days

2.2. Are you pregnant? ☐ Yes ☐ No ☐ Not applicable

2.3. Which country have you been living in the past 1 year?

____

2.4. Did you travel outside your current residential area in the past 1 year? ☐ Yes ☐ No

IF Yes, Which country(s) did you visit? (latest first)

____

2.5. Have you performed Hajj or Umrah in the past year?

☐ Yes ☐ No ☐ Don't recall

2.6. Please tell us if you have any of the following health conditions?

(Tick in appropriate box)

☐ Chronic kidney disease ☐ Chronic lung disease

☐ Chronic liver disease ☐ Cardiovascular disease

☐ Hypertension ☐ Cancer

☐ Immunosuppressive illness ☐ Diabetes

☐ Stroke ☐ No underlying health condition

☐ Not listed

IF Not listed, Please tell us the condition you have:

____

2.7.Do you currently smoke any tobacco product such as cigarettes,cigars or pipes?

☐ Yes ☐ No

IF No, did you ever smoke tobacco product in the past?

☐ Yes ☐ No

2.8. Are you currently on any medication?

☐ Yes ☐ No

IF Yes, Please tell us the name(s) of the medication(s):

____

2.9. Have you ever been treated for TB?

☐ Yes ☐ No ☐ Don't know

(IF No/Don't know, Please proceed to question 2.13.)

2.10. How long did you receive TB treatment for?

☐ ≤1month ☐ 2-5month ☐ 6-12month

☐ ≥12 month ☐ Can't recall

2.11. Did you complete your TB treatment?

☐ Yes ☐ No

2.12. Are you currently receiving TB treatment?

☐ Yes ☐ No

2.13.Have you recently lived in the same household with an adult with cough (Lasted up to 2 weeks)?

☐ Yes ☐ No

2.14. Has any of your close contacts been diagnosed or treated for TB?

☐ Yes ☐ No ☐ Don't know

2.15. Do you currently cough up blood? ☐ Yes ☐ NO

Data Collector's Name: ____________________ Date: DD / MM /2016

Signature:

Cont.. Appendix 1 Data collection form for non-hospitalised pilgrims symptomatic for cough

Pilgrim's Incoming Flight No.: ____

Date of Arrival: DD / MM /2016

Port of Entry: ____

Port of Departure: ____

Pilgrim's Contact Details:

____

____

Muttawef's Name: ____

Muttawef's Contact No.: ____

Data Collector's Name: ______________________ Date: DD / MM /2016

Signature:

Appendix 2: Data collection form for hospitalised pilgrims symptomatic for cough

Verbal consent obtained (check √) ☐ **Name** ______________________________ **Signature** ________________________

Section (1): Demographics Data

1.1.Passport page copy attached: ☐ Yes ☐ No

(If Yes, Please proceed to question 1.7)

1.2.Full Name: ________________________

1. 3.Gender: ☐ Male ☐ Female

1. 4.Date of birth: DD / MM / YYYY

OR Age (in years): ___________________________________

1.5. Nationality: _____________________________________

1.6. Passport / Iqama / ID No.: _________________________

1.7. What is the highest level of education you have achieved?

(Tick in the appropriate box)

☐ University/Higher education ☐ Secondary education

☐ Primary education ☐ No formal education

1.8. Which of these best describes your job?

(Tick in the appropriate box)

☐ Health care worker ☐ Laboratory personnel

☐ Refugee camp worker ☐ Prison staff

☐ Miner ☐ None of the above

Section (2): Health Conditions & Epidemiological Risk Factors

2.1. How long have you had this cough for? __________ days

2.2. Are you pregnant? ☐ Yes ☐ No ☐ Not applicable

2.3. Which country have you been living in the past 1 year?

____

2.4. Did you travel outside your current residential area in the past 1 year? ☐ Yes ☐ No

IF Yes, Which country(s) did you visit? (latest first)

____

2.5. Have you performed Hajj or Umrah in the past year?

☐ Yes ☐ No ☐ Don't recall

2.6. Please tell us if you have any of the following health conditions?

(Tick in appropriate box)

☐ Chronic kidney disease ☐ Chronic lung disease

☐ Chronic liver disease ☐ Cardiovascular disease

☐ Hypertension ☐ Cancer

☐ Immunosuppressive illness ☐ Diabetes

☐ Stroke ☐ No underlying health condition

☐ Not listed

IF Not listed, Please tell us the condition you have:

____

2.7.Do you currently smoke any tobacco product such as cigarettes,cigars or pipes?

☐ Yes ☐ No

IF No, did you ever smoke tobacco product in the past?

☐ Yes ☐ No

2.8. Are you currently on any medication?

☐ Yes ☐ No

IF Yes, Please tell us the name(s) of the medication(s):

____

2.9. Have you ever been treated for TB?

☐ Yes ☐ No ☐ Don't know

(IF No/Don't know, Please proceed to question 2.13.)

2.10. How long did you receive TB treatment for?

☐ ≤1month ☐ 2-5month ☐ 6-12month

☐ ≥12 month ☐ Can't recall

2.11. Did you complete your TB treatment?

☐ Yes ☐ No

2.12. Are you currently receiving TB treatment?

☐ Yes ☐ No

2.13.Have you recently lived in the same household with an adult with cough (Lasted up to 2 weeks)?

☐ Yes ☐ No

2.14. Has any of your close contacts been diagnosed or treated for TB?

☐ Yes ☐ No ☐ Don't know

2.15. Do you currently cough up blood? ☐ Yes ☐ NO

Data Collector's Name: _________________________________ Date: DD / MM /2016

Signature:

Cont. Appendix 2: Data collection form for hospitalised pilgrims symptomatic for cough

Section (3): Clinical Data for Hospitalized Pilgrims

3.1. Date of admission: DD / MM /2016

3.2. File number:

3.3. Which ward was the patient admitted to on admission?

☐ Emergency room (ER) ☐ Intensive care unit (ICU) ☐ General ward ☐ Isolation ward

☐ Others, please specify: ______________________________

3.4. What is the duration of current illness?

☐ <1 week ☐ 1-2 weeks ☐ 3-4 weeks ☐ > 4 weeks

3.5. Was the patient tested for TB?

☐ Yes ☐ No ☐ Not Applicable

IF YES, What TB test(s) was done to the patient?

☐ Sputum AFB ☐ Chest x-ray ☐ GeneXpert MTR/RIF test ☐ Sputum culture

☐ Others, please specify: ______________________________

3.6. Was the test result positive for TB?

☐ Yes ☐ No ☐ Not Applicable

3.7. Does the patient have MDRT?

☐ Yes ☐ No ☐ Not Applicable

3.8. Is the patient currently receiving TB treatment?

☐ Yes ☐ No ☐ Not Applicable

IF YES, What is the treatment regime? ___________________________ Start Date: DD / MM / YYYY

3.9. What is the admission diagnosis of this patient? ______________________________

3.10. What is the final diagnosis for this patient (if applicable)? ______________________________

3.11. What is the final outcome of the case:

☐ Discharged ☐ Deceased ☐ Defaulted

☐ Referred (name of the facility): ____________________ ☐ Still at the hospital by the end of the study

Section (4): Study's TB Testing Results

4.1. Date of testing: DD / MM / YYYY

4.2. GeneXpert MTB/RIF test results: ☐ Positive ☐ Negative ☐ Not Applicable

IF Positive, was it positive for MDRT? ☐ Yes ☐ No ☐ Not Applicable

Pilgrim's Incoming Flight No.:______________________ Date of Arrival: DD / MM /2016

Port of Entry: ______________________________ Port of Departure: ______________________________

Pilgrim's Contact Details: ____

____

Muttawef's Name: ______________________________ Muttawef's Contact No.: ______________________________

Data Collector's Name: ______________________________ Date: DD / MM /2016

Signature:

Appendix 3: Data collection form for management of hospitalized patients with TB

4.3. Has the TB **suspected** patient been questioned about history of possible close contact with patients with active pulmonary TB?
- [ ] Yes
- [ ] No
- [ ] Don't know

4.4. Has the TB **suspected** patient been questioned about his/her TB history? (i.e previous TB diagnosis, previous TB treatment)
- [ ] Yes
- [ ] No
- [ ] Don't know

4.5. The patient is a **confirmed** TB case and receiving TB treatment before admission?
- [ ] Yes
- [ ] No

IF YES, specify the following:

Type of TB:

____

Treatment regime: ______________________________

Date of start of treatment: DD / MM / YYYY

4.6. Has the TB **suspected** patient been questioned about TB risk factors:
- [ ] HIV status
- [ ] Occupation
- [ ] Country of origin
- [ ] Not questioned
- [ ] **Other, specify:** ______________________________

4.7. Number of visits to the healthcare facility before screening/diagnosis tests were ordered for the patient?

specify: ____________________
- [ ] Don't know

4.8. Which screening/diagnostic tests were ordered for the TB **suspected** patient?
- [ ] TST (Tuberculin skin tests)
- [ ] Blood culture
- [ ] GeneXpert MTB/RIF test
- [ ] Sputum culture
- [ ] Sputum smear test
- [ ] Chest X-ray
- [ ] Liver function tests
- [ ] CBC
- [ ] IGRA (Interferon Gamma Release Assay)
- [ ] **Other, specify:** ______________________________

4.9. Time between patient registration/arrival and the order of screening/diagnostic tests?
- [ ] <1 hr
- [ ] 1-12 hr
- [ ] >12-24 hr
- [ ] >24 hr
- [ ] NA

4.10. Where was the TB **suspected** patient admitted while awaiting diagnosis?
- [ ] General ward
- [ ] ER
- [ ] Isolation room with HEPA
- [ ] ICU
- [ ] Negative pressure isolation room
- [ ] Not admitted
- [ ] **Other, specify:** ______________________________

4.11. Time between order of screening/diagnostic tests and **confirmation** of active pulmonary TB?
- [ ] < 1 day
- [ ] 1-2 days
- [ ] 3-7 days
- [ ] >7 days

Date/time of confirmation of pulmonary TB:

Date: DD / MM / YYYY **Time:** ______________

4.12. Where was the **confirmed** pulmonary TB patient admitted in the healthcare facility?
- [ ] General ward
- [ ] ER
- [ ] Isolation room with HEPA
- [ ] ICU
- [ ] Negative pressure isolation room
- [ ] Not admitted
- [ ] **Other, specify:** ______________________________

4.13. How long was the **confirmed** pulmonary TB patient in the healthcare facility from arrival to isolation?
- [ ] <1 day
- [ ] 1-2 days
- [ ] 3-7 days
- [ ] >7 days
- [ ] NA (Not applicable)

4.14. How long was the **confirmed** pulmonary TB patient in the healthcare facility from arrival to discharge?
- [ ] <1 day
- [ ] 1-2 days
- [ ] 3-7 days
- [ ] >7 days
- [ ] NA (Not applicable)

4.15. Did the patient receive antibiotic treatment before **confirmation** of pulmonary TB?
- [ ] Yes
- [ ] No

IF YES, specify:

The antibiotic treatment:

____

4.16. Was the **confirmed** pulmonary TB patient prescribed a treatment regime?
- [ ] Yes
- [ ] No

IF YES, specify: Treatment: ______________________

Duration: ______________________

Start date: DD / MM / YYYY

4.17. Was the **confirmed** pulmonary TB patient reported to his country's medical office?
- [ ] Yes
- [ ] No
- [ ] Don't know

4.18. Was the **confirmed** pulmonary TB patient referred for further treatment after Hajj?
- [ ] Yes
- [ ] No
- [ ] Don't know

4.19. Was the **confirmed** pulmonary TB patient given enough TB treatment to last until his arrival to his/her country of origin?
- [ ] Yes
- [ ] No
- [ ] Don't know

4.20. Was the **confirmed** pulmonary TB patient reported to the Ministry of Health preventative medicine department?
- [ ] Yes
- [ ] No
- [ ] Don't know

Data Collector's Name: ______________________________ Date: DD / MM /2016

Signature:

Cont. Appendix 3: Data collection form for management of hospitalized patients with TB

4.21. Was the **confirmed** pulmonary TB patient discharged to complete his Hajj rites?
☐ Yes ☐ No ☐ Don't know
IF YES,
☐ In an ambulance with other TB patient.
☐ In an ambulance alone.
☐ Without medical assistance.
☐ **Other, specify**: ______________________________

Section (5): Data on Multidrug Resistant TB (MDR-TB)

5.1. Has the **confirmed** TB case been questioned regarding previous TB treatment?
☐ Yes ☐ No ☐ NA ☐ Don't Know

5.2. Has the **confirmed** TB case been questioned regarding defaulting from previous TB treatment?
☐ Yes ☐ No ☐ NA ☐ Don't Know

5.3. Has the **confirmed** TB case been questioned regarding relapse after previous TB treatment?
☐ Yes ☐ No ☐ NA ☐ Don't Know

5.4. Was the patient **confirmed** to have **MDR-TB**?
☐ Yes ☐ No ☐ NA

IF YES, Date: DD / MM / YYYY **Time:** ____________

5.5. Was the patient **confirmed** to have **XDR-TB**?
☐ Yes ☐ No ☐ NA

IF YES, Date: DD / MM / YYYY **Time:** ____________

5.6. Where was the **confirmed** pulmonary **MDR-TB/XDR-TB** patient housed in the healthcare facility?
☐ General ward
☐ Isolation room with HEPA
☐ Negative pressure isolation room
☐ NA
☐ **Other, specify**:________________________________
☐ ER
☐ ICU
☐ Not admitted

Data Collector's Name: ______________________________ Date: DD / MM /2016

Signature:

Appendix 4: Data collection form for the knowledge, attitude and practice survey of healthcare workers regarding TB

Section (1) : Healthcare worker (HCW) information

1.1. Gender :
- ☐ Male
- ☐ Female

1.2. Age (Years): ____________________

1.3. Nationality : ____________________

1.4. Highest level of education:
- ☐ Diploma
- ☐ Bachelor
- ☐ Master
- ☐ Doctorate/Speciality certificate
- ☐ **Other Please Specify** ____________________

1.5. Occupation:
- ☐ Physician : **(Please Specify**)
  - ☐ Resident
  - ☐ Specialist
  - ☐ Consultant
  - ☐ General practitioner
  - ☐ **Other (please specify)** ____________________
- ☐ Nurse : **(Please Specify**)
  - ☐ Infection control nurse
  - ☐ **Other (please specify)** ____________________

Other :
- ☐ Laboratory / Diagnostics
- ☐ Pharmacist
- ☐ **Other (please specify)** ____________________

1.6. Ward stationed in during your <u>non-Hajj</u> health facility (Tick all that apply) :
- ☐ ICU
- ☐ Surgical ward
- ☐ ER
- ☐ Pediatric ward
- ☐ Medical ward
- ☐ Maternity (O&G) ward
- ☐ Isolation ward
- ☐ **Other (please specify)** ____________________

1.7. How long have you been working in this current position?
- ☐ <1 year
- ☐ >5-10 years
- ☐ 1-5 years
- ☐ >10 years

1.8. Do you deal with pulmonary TB patients in your <u>non-Hajj</u> health facility?
- ☐ Yes
- ☐ No

1.9. Ward stationed in during <u>Hajj</u> :
- ☐ ICU
- ☐ ER
- ☐ Medical ward
- ☐ Surgical ward
- ☐ Pediatric ward
- ☐ Maternity (O&G) ward
- ☐ **Other (please specify)** ____________________

1.10. During your <u>Hajj</u> assignment, did you deal with pulmonary TB cases?
- ☐ Yes
- ☐ No

Section (2) : TB Knowledge

2.1. In the past 12 months, have you attended a lecture / seminar / workshop on TB?
- ☐ Yes
- ☐ No
- ☐ Don't know

2.2. TB falls under:
- ☐ Viral infection
- ☐ Bacterial Infection
- ☐ Don't know

2.3. Which of these is/are main symptom(s) of pulmonary TB? (Tick all that apply)
- ☐ Cough ≥3 weeks
- ☐ Pain with urination
- ☐ Fever/chills
- ☐ Diarrhea
- ☐ Dizziness
- ☐ Chest pain
- ☐ Tiredness/fatigue
- ☐ Loss of appetite
- ☐ Cough with blood
- ☐ Memory loss
- ☐ Weight loss
- ☐ Night sweats
- ☐ Headache
- ☐ Blurry vision
- ☐ Don't know

2.4. Which of the following is/are diagnostic test(s) for pulmonary TB? (Tick all that apply) :
- ☐ Mantoux tuberculin skin tests (TST)
- ☐ Liver function test
- ☐ Sputum culture
- ☐ Complete Blood Count (CBC)
- ☐ Urine examination
- ☐ Blood Culture
- ☐ GeneXpert MTB/RIF test
- ☐ Chest x-ray
- ☐ Sputum Acid-fast bacilli (AFB) smear
- ☐ Don't know
- ☐ Interferon Gamma Release Assay (IGRA)

2.5. Which of the following is/are the mode of pulmonary TB transmission? (Tick all that apply)
- ☐ Blood transmission
- ☐ Sneezing
- ☐ Coughing
- ☐ Kissing
- ☐ Sharing food or drink
- ☐ Shaking hand
- ☐ Touching surfaces contaminated with *M. tuberculosis*

2.6. Which of the following is/are screening test(s) for latent TB infection? (Tick all that apply)
- ☐ Mantoux tuberculin skin tests (TST)
- ☐ Liver function test
- ☐ Complete Blood Count (CBC)
- ☐ Sputum culture
- ☐ Urine examination
- ☐ Blood Culture
- ☐ GeneXpert MTB/RIF test
- ☐ Chest x-ray
- ☐ Sputum Acid-fast bacilli (AFB) smear
- ☐ Don't know
- ☐ Interferon Gamma Release Assay (IGRA)

2.7. What percentage of active pulmonary TB will be positive for TB on smear microscopy :
- ☐ 10%
- ☐ 50%
- ☐ 20%
- ☐ 80%
- ☐ Don't know

Cont. Appendix 4: Data collection form for the knowledge, attitude and practice survey of healthcare workers

2.8. What method of sputum sample collection is the most useful for pulmonary TB diagnosis?
- 3 (spot, morning, spot) samples
- 1 spot sample
- 2 spot, 1 spot samples
- 2 spot samples
- Don't know

2.9. Which of these is/are first line anti-TB drugs: (Tick all that apply)
- Isoniazid (INH)
- Kanamycin (KAN)
- Rifampicin (RIF)
- Ethambutol (EMB)
- Ciprofloxacin (CIP)
- Pyrazinamide (PZA)
- Flevofloxacin (LEV)
- Amikacin (AMK)
- Capreomycin (CAP)
- Don't know

2.10. Which of these is/are a second-line anti-TB drugs: (Tick all that apply)
- Isoniazid (INH)
- Kanamycin (KAN)
- Rifampicin (RIF)
- Ethambutol (EMB)
- Ciprofloxacin (CIP)
- Pyrazinamide (PZA)
- Flevofloxacin (LEV)
- Amikacin (AMK)
- Capreomycin (CAP)
- Don't know

2.11. Multidrug-resistant tuberculosis (MDR-TB) is caused by bacteria resistant to:
- Isoniazid
- Rifampicin
- at least Isoniazid and Rifampicin
- Ethambutol
- at least Ciprofloxacin and Kanamycin
- Don't know
- All of the above

2.12. Extensively drug-resistant TB (XDR-TB) is:
- MDR-TB resistant to any fluoroquinolone and at least one of three injectable second-line drugs
- TB resistant to any fluoroquinolone and at least one of three injectable second-line drugs
- TB resistant to all first-line anti-TB drug
- Don't know

2.13. The standard treatment for new patient with drug-sensitive TB is:
- 1-3 Months
- 4-<6 Months
- 6-9 Months
- >12 Months
- Don't know

2.14. HIV patient are more vulnerable to contracting TB :
- True
- False
- Don't Know

2.15. Pulmonary TB is a curable disease :
- True
- False
- Don't Know

2.16. MDR-TB is a curable disease :
- True
- False
- Don't Know

2.17. People that have received bacilli Calmette-Guerin (BCG) vaccination do not develop active TB :
- True
- False
- Don't Know

2.18. Airborne is a mode of transmission of pulmonary TB:
- True
- False
- Don't Know

2.19. Patient with latent TB can spread the disease:
- True
- False
- Don't Know

2.20. Patient with latent TB have a positive reaction to TST or IGRA:
- True
- False
- Don't Know

2.21. Patient with TB usually become noninfectious soon after initiating appropriate treatment:
- True
- False
- Don't Know

2.22. Only patient with active TB can spread the disease:
- True
- False
- Don't Know

2.23. Which Personal Protective Equimement (PPE) you should use when dealing with a patient with active pulmonary TB:
- Surgical mask
- N95 respirator
- No PPE is needed
- Don't know

2.24. Using PPE to protect HCWs from TB is important:
- Yes
- No
- Don't know

Section (3): Attitude towards TB/TB patients

3.1.Would you be willing to work in a TB clinic/ward?
- Yes
- No

3.2.Would you resign from work if you are posted to a TB clinic/ward?
- Yes
- No

3.3.Would you be willing to be screened for TB if you had suggestive symptoms?
- Yes
- No

3.4.Would you be willing to teach patients and co-workers about TB prevention?
- Yes
- No

Cont. Appendix 4: Data collection form for the knowledge, attitude and practice survey of healthcare workers

3.5. Do you think all TB patients should be isolated for treatment?

☐ Yes ☐ No ☐ Don't know

3.6. It is ok to allow a TB patient to leave the hospital soon after initiating appropriate treatment:

☐ Yes ☐ No ☐ Don't know

3.7. Would you be willing to attend seminars on TB:

☐ Yes ☐ No

3.8. Would you recommend the suspension of treatment if a TB patient is feeling better?

☐ Yes ☐ No ☐ Not applicable

3.9. Would you start TB treatment for a TB patient before diagnosis is confirmed if a suspected TB patient is very ill?

☐ Yes ☐ No ☐ Not applicable

3.10. Would you use a face mask when dealing with a pulmonary TB patient even when it is uncomfortable:

☐ Yes ☐ No

3.11. Would you be willing to teach patient how to collect sputum sample:

☐ Yes ☐ No ☐ Not applicable

3.12. Would you trust the result the laboratory provides you on sputum cultures:

☐ Yes ☐ No ☐ Not applicable

3.13. I would not accept to examine/treat a TB patients:

☐ Yes ☐ No

3.14. I have a very low risk of acquiring TB from my patients:

☐ Yes ☐ No ☐ Don't know

3.15. I worry about acquiring active TB disease while at work:

☐ Yes ☐ No

Section (4): TB Practice

4.1. I usually perform hand hygiene and wear PPE before contact with pulmonary TB patient/TB samples:

☐ Yes ☐ No ☐ Not applicable

4.2. I usually wear N95 respirator when caring for patient with pulmonary TB/working on TB samples:

☐ Yes ☐ No ☐ Not applicable

4.3. I request sputum tests when I suspect active TB:

☐ Yes ☐ No ☐ Not applicable

4.4. Always put the patient with active TB in an isolated room:

☐ Yes ☐ No ☐ Not applicable

4.5. I open windows when possible in TB patients rooms to increase natural ventilation:

☐ Yes ☐ No ☐ Not applicable

4.6. I order HIV test when I diagnose active TB:

☐ Yes ☐ No ☐ Not applicable

4.7. Always put the patient with known TB separated from HIV patients:

☐ Yes ☐ No ☐ Not applicable

4.8. Sometimes I use wet or soiled N95 respirator:

☐ Yes ☐ No ☐ Not applicable

4.9. I always make sure that samples are sputum and not saliva before sending them to laboratory/before testing in the laboratory:

☐ Yes ☐ No ☐ Not applicable

4.10. I commence anti-TB drugs on suspect TB cases before lab confirmation:

☐ Yes ☐ No ☐ Not applicable

4.11. I request contact tracing for all confirmed TB cases:

☐ Yes ☐ No ☐ Not applicable

4.12. I request liver function tests before starting anti-TB treatment:

☐ Yes ☐ No ☐ Not applicable

4.13. I start contacts of active TB cases who are positive for IGRA/TST tests on Isoniazid /Rifampicin prophylaxis:

☐ Yes ☐ No ☐ Not applicable

Appendix 5: IRB approval (King Fahad Medical City, Riyadh, KSA)

Kingdom of Saudi Arabia
Ministry of Health
King Fahad Medical City
(162)

وزارة الصحة
مدينة الملك فهد الطبية
King Fahad Medical City

المملكة العربية السعودية
وزارة الصحة
مدينة الملك فهد الطبية
(١٦٢)

IRB Registration Number with KACST, KSA:	H-01-R-012
IRB Registration Number with OHRP/NIH, USA:	IRB00010471
Approval Number Federal Wide Assurance NIH, USA:	FWA00018774

September 4, 2016
IRB Log Number: 16-329E
Department: External
Category of Approval: EXPEDITED

Dear Dr. Badriah Alotaibi,

I am pleased to inform you that submission dated September 4, 2016 for the study titled '**Tuberculosis during the Hajj mass gathering: prevalence, prevention, and management**' was reviewed and was approved according to Good Clinical Practice guidelines.

Please be informed that in conducting this study, you as the Principal Investigator are required to abide by the rules and regulations of the Government of Saudi Arabia, the KFMC/IRB policies and procedures, and the ICH Good Clinical Practice guidelines. Further, you are required to submit a Progress Report before August 4, 2017; it can be reviewed by the IRB without lapse of approval. The approval of this proposal will automatically be suspended on September 4, 2017 pending the acceptance of the Progress Report. You also need to notify the IRB as soon as possible in the case of:

1. Any amendments to the project;
2. Termination of the study;
3. Any serious unexpected adverse events (within two working days);
4. Any event or new information that may affect the benefit/risk ratio of the proposal.

Please observe the following:

1. Personal identifying data should only be collected when necessary for research;
2. The data collected should only be used for this proposal;
3. Data should be stored securely so that a few authorized users are permitted access to the database;
4. Secondary disclosure of personal identifiable data is not allowed;
5. Copy of the Consent Form should be kept in the Research Subject's Medical Record and the consent process should be documented in the medical record;
6. Copy of the pharmacy clearance (IDS) must be in the medical record.

Please be advised that regulations require that you submit a progress report on your research every 6 months. You are also required to submit any manuscript resulting from this research for approval by IRB before submission to journals for publication.

Appendix 5: IRB Approval (King Fahad Medical City, Riyadh, KSA)

Kingdom of Saudi Arabia
Ministry of Health
King Fahad Medical City
(162)

مدينة الملك فهد الطبية
King Fahad Medical City

المملكة العربية السعودية
وزارة الصحة
مدينة الملك فهد الطبية
(١٦٢)

IRB Registration Number with KACST, KSA: H-01-R-012
IRB Registration Number with OHRP/NIH, USA: IRB00010471
Approval Number Federal Wide Assurance NIH, USA: FWA00018774

August 8, 2017
IRB Log Number: 16-329E
Category of Approval: EXPEDITED

Dear Dr. Badriah Alotaibi,

I am pleased to inform you that the **renewal** request for your study titled **'Tuberculosis during the Hajj mass gathering: prevalence, prevention, and management'** dated August 7, 2017 was reviewed and was approved for 1 year with effect from the date of this letter and under the conditions of the original approval.

You are required to submit a Progress report every 6 months starting from the date of approval. Approvals are for 1 year and are renewable on submission of satisfactory 6-monthly reports. The approval of this proposal will automatically be **suspended on August 8, 2018** pending the acceptance of the end-of-year Progress Report.

We wish you well as you proceed with the study and request you to keep the IRB informed of the progress on a regular basis, using the IRB log number above.

As a researcher you are required to have current and valid certification on protection human research subjects that can be obtained by taking a short online course at the US NIH site or the Saudi NCBE site followed by a multiple choice test. Please submit your current and valid certificate for our records. Failure to submit this certificate shall a reason for suspension of your research project.

If you have any further questions feel free to contact me.

Sincerely yours,

Prof. Omar H. Kasule
Chairman, Institutional Review Board (IRB)
King Fahad Medical City, Riyadh, KSA
Tel: + 966 1 288 9999 Ext. 26913
E-mail: okasule@kfmc.med.sa

K F M C Approved 0 8 AUG 2017 I R B

Appendix 5: IRB Approval (King Fahad Medical City, Riyadh, KSA)

Kingdom of Saudi Arabia
Ministry of Health
King Fahad Medical City
(162)

وزارة الصحة
مدينة الملك فهد الطبية
King Fahad Medical City

المملكة العربية السعودية
وزارة الصحة
مدينة الملك فهد الطبية
(١٦٢)

IRB Registration Number with KACST, KSA:	H-01-R-012
IRB Registration Number with OHRP/NIH, USA:	IRB00010471
Approval Number Federal Wide Assurance NIH, USA:	FWA00018774

August 7, 2018
IRB Log Number: 16-329E
Category of Approval: EXPEDITED

Dear Dr. Badriah Alotaibi,

I am pleased to inform you that the **renewal** request for your study titled **'Tuberculosis during the Hajj mass gathering: prevalence, prevention, and management'** dated August 6, 2018 was reviewed and was approved for 1 year with effect from the date of this letter and under the conditions of the original approval.

You are required to submit a Progress report every 6 months starting from the date of approval. Approvals are for 1 year and are renewable on submission of satisfactory 6-monthly reports. The approval of this proposal will automatically be **suspended on August 7, 2019** pending the acceptance of the end-of-year Progress Report.

We wish you well as you proceed with the study and request you to keep the IRB informed of the progress on a regular basis, using the IRB log number above.

As a researcher you are required to have current and valid certification on protection human research subjects that can be obtained by taking a short online course at the US NIH site or the Saudi NCBE site followed by a multiple choice test. Please submit your current and valid certificate for our records. Failure to submit this certificate shall a reason for suspension of your research project.

If you have any further questions feel free to contact me.

Sincerely yours,

Omar Kasule

K F M C
Approved
07 AUG 2018
I R B

Prof. Omar H. Kasule
Chairman, Institutional Review Board (IRB)
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