

## Review

# Tuberculosis in Saudi Arabia: the journey across time

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### Abstract

Saudi Arabia is the third-largest Arab country with a moderate annual burden of tuberculosis. However, tuberculosis (TB) is among several infectious diseases that have not been brought under control, despite the government's considerable efforts. This is clearly evidenced by the ongoing transmission of several imported and indigenous clades of *Mycobacterium tuberculosis*. In addition, the country faces the threat from rising proportions of extrapulmonary TB, non-tuberculous mycobacterial infections, and drug resistance. Furthermore, the country falls behind the global targets set by World Health Organization for the success rate of TB treatment. The country needs more population-based research studies, centralized and easily accessible clinical data registries, and centralized research and diagnostic facilities. This review focused on the trends of mycobacterial infections and on future proposals to improve TB control measures in Saudi Arabia.

**Key words:** Saudi Arabia; tuberculosis; epidemiology; transmission dynamics; migrants.

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### Introduction

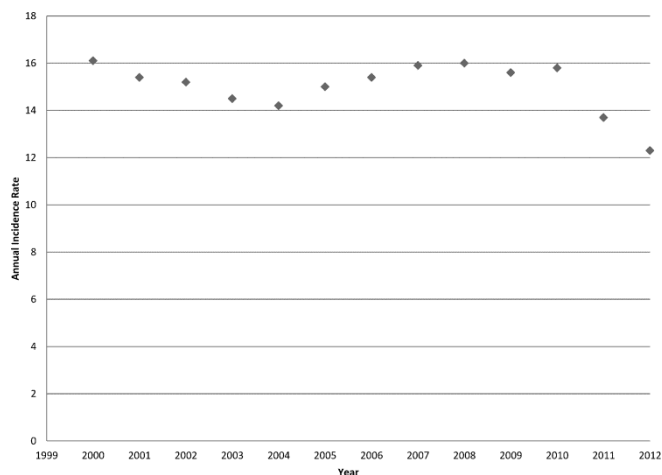
Tuberculosis (TB) is a re-emerging infectious disease and a substantial public health problem globally despite improvements in diagnosis, treatment, and control. The 2012 global report showed a development of 8.6 million new cases and 1.3 million deaths related to TB, including 320,000 deaths among human immunodeficiency virus (HIV) co-infected patients. However, a fall in new TB cases and drop in mortality to 45% was noticed worldwide, despite of the challenges from drug resistance and HIV co-infection [1].

### Epidemiology of tuberculosis in Saudi Arabia

Saudi Arabia is the third-largest country in the Middle East by land area, constituting the bulk of the Arabian Peninsula, and is the third-largest Arab country. As of 2012 statistical data, the total population is 29,195,895, consisting of 19,838,448 Saudi nationals and 9,357,447 non-Saudi nationals [2]. According to the World Health Organization (WHO), in 2012, Saudi Arabia reported an annual TB incidence rate of 18/100,000 population and remains a moderate TB burden country [1]. Figure 1 shows the changes in incidence rates of tuberculosis in the country since 2000.

The published data show that TB in Saudi Arabia is still not fully controlled despite the government's efforts to eradicate the disease. Even though the directly observed therapy short course (DOTS) program in the country was implemented in 1999 as part of the national tuberculosis control program (NTP), the treatment success rate (62%) still remains below the international target set by the WHO (85%) [3]. In addition, the recent case detection rate also remains at 87% [1]. In the last 10 years, the mortality rates among TB patients in the country show a decreasing trend (7.2% to 6.1%) among Saudis and a steady state among non-Saudis (~5.4%). Nonetheless, advancing age and male gender are still risk factors for higher mortality among Saudi nationals, and being female is a risk factor among non-Saudis. In addition, HIV seropositivity, smear positivity, and previous history of TB treatment were also predisposing factors behind elevated mortality [4]. The incidence rate of TB is two or three times higher in the immigrant population compared with the local population [5]. Furthermore, annual statistical data from the Ministry of Health showed a declining trend of incidence among non-Saudis and a stable trend among Saudi nationals (Figure 2).

**Figure 1.** Incidence rate of TB during 2000–2012 [5,8]



**Regional difference in annual TB case notifications**

Regional differences in the incidence rate of TB in the country have been clearly demonstrated in several studies [5-8]. Some regions showed a decrease in TB prevalence, whereas other regions with a high number of immigrants showed an increase in TB incidence [9]. Figure 3 shows the trend of reported TB cases during 2006–2012. Clear evidence of higher TB incidence in the western region, followed by the central region, has been observed during the last seven years. These two regions have the most populated provinces, hosting the majority of the immigrant population.

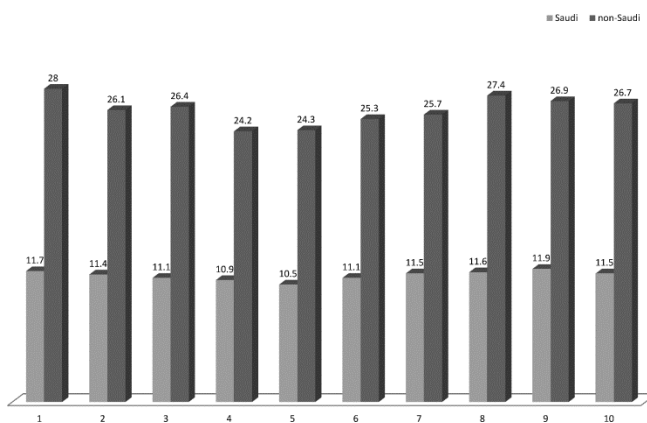
**TB in Gulf Cooperation Council (GCC) states and the Arabian Peninsula**

Among the GCC states, Saudi Arabia reports the highest number of notified cases annually. However, compared with the other five member states except United Arab Emirates and Oman, the real incidence rate for 100,000 population is low. Interestingly, extrapulmonary TB (EPTB) is reported in all these states above the level (> 25%) of developed countries. The treatment success rate in Saudi Arabia is still behind the global target, though the other states have already reached the targets [1]. Generally, the Arabian Peninsula, which includes Iraq, Jordan, and Yemen along with the GCC states, has a moderate TB burden. However, Saudi Arabia remains at the seventh position only in terms of prevalence [1].

**Pulmonary TB and extrapulmonary TB**

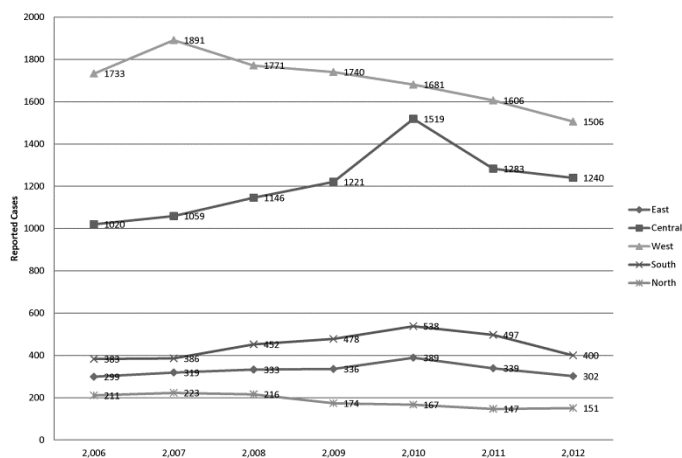
Abouzeid *et al.* reported an increasing trend of pulmonary TB case notification in the past ten years in Saudi Arabia [5]. This study showed that smear-positive pulmonary TB is consistently reported

**Figure 2.** Tuberculosis incidence rate among Saudi and non-Saudi nationals during 2000–2009 [5]



(44.9%–50.2%) in Saudi nationals, whereas immigrants showed considerably higher rates (52.1%–62.6%) than the global rate of 45.5%. However, smear-negative pulmonary TB is found less frequently than in other global regions among Saudis and non-Saudis. The pulmonary smear-positive TB among both Saudis and non-Saudis showed an upward trend (11.8% to 20.2%); this may indicate the impact of intensifying the diagnostic capabilities and other implementations done under the NTP [5]. However, the Ministry of Health of Saudi Arabia reported a decrease in pulmonary TB incidence in previous years (Figure 4).

**Figure 3.** Regional case notification of TB during 2006–2012 [8]



The notified new cases of TB in the five geographical regions representing 13 provinces of the country have been explained. The western region includes the provinces Makkah, Medina; the northern region includes Tabuk, Hail, Al-Jouf; the northern borders include South-Asir, Jizan, Najran and al-Baha; the central region includes Riyadh and Al-Qassim.

In Saudi Arabia, the level of extrapulmonary TB (EPTB) is stable, 29.3% in 2006 compared to 28.4% in 2012 [8,10]. According to the WHO, the Eastern Mediterranean region (which includes Saudi Arabia) has the highest rate of EPTB (22%) globally. In this context, Saudi Arabia always stays above the average (28% in 2012) [1]. Saudi nationals show a significant predominance of EPTB compared with the immigrant population. The infection rate has always been above 50%, but there was a clear rise (from 52% and 59.8%) between 2006 and 2011 [8,10]. A recent retrospective analysis showed an upward trend of EPTB among Saudis (9%), while non-Saudis showed a downward trend (-17.2%) [5].

Another recent study conducted at King Faisal Specialist Hospital and Research Centre, Riyadh, on a nationwide data collection to determine the related demographical and clinical factors of EPTB showed a similar dominance of the autochthonous population in terms of incidence rate. This study revealed a domination of male (57.5%) gender. This is distinctly different from the predominance of EPTB in the rest of the world. Apart from the predominance of TB in lymph nodes and central nervous and gastrointestinal systems, TB was largely reported, particularly among Saudi nationals. Nonetheless, a huge diversity in the clinical manifestations of EPTB in the country has been reported previously in various institutions [11-13]. Figure 4 details the incidence rate of extrapulmonary TB for a period of eight years in the country, as reported by the Ministry of Health.

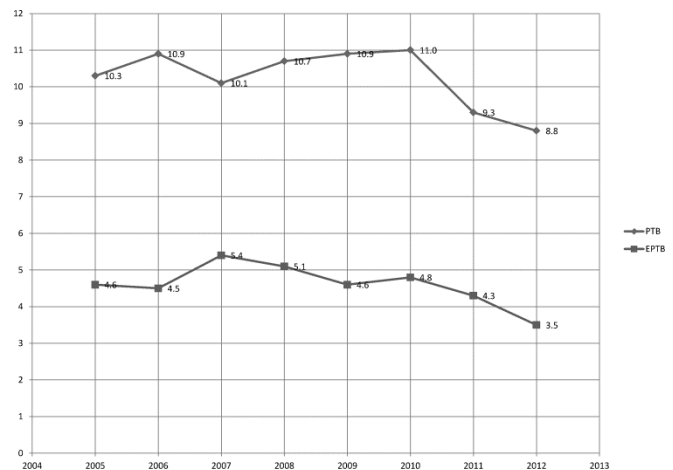
The reasons behind the higher incidence of EPTB in Saudi Arabia are still unknown. The same trend has also been found in all the neighboring countries [1,14]. According to the WHO, the Eastern Mediterranean region shows the highest incidence of EPTB in the world [1]. One possible assumption is that this high rate may be related to the high probability of reactivation of latent infection, particularly among migrant-receiving countries [15]. On the other hand, another unexplored possibility is related to the host genetic factors, as all the Arab counties are prone to genetic disorders and related complications mainly because of the high rate of consanguinity.

## Factors influencing TB transmission in Saudi Arabia

### *Hajj and Umrah*

Hajj is the most sacred pilgrimage to Makkah followed by a visit to the other holy city, Medina. Hajj annually gathers approximately three million Muslims from around the world. Umrah is another Islamic

**Figure 4.** Incidence rate of pulmonary and extrapulmonary TB during 2005–2012 [8]



ritual, which can be performed throughout the year by visiting both holy cities; approximately five to seven million visitors arrive annually. The intense congestion of pilgrims, the majority of whom are from highly endemic places of TB in Asia and Africa, overcrowding, supports the transmission of infectious diseases, including TB [16-18]. Transmission is also influenced by the age of the pilgrims, who may be suffering from underlying diseases or conditions, and is exacerbated by the high level of physical exertion.

### *Immigrants*

In addition to its 20 million citizens, Saudi Arabia hosts 9.9 million (32.4% of the total population) immigrant workers from all over the world [2]. These immigrant workers are scattered all over the country and are concentrated in major cities, most originating from TB-endemic countries in Asia and Africa. In a recent study, the collated data from non-Saudi TB patients showed a higher presence of Africans (37.5%), South Asians (27.8%), and Southeast Asians (23.5%), with a considerable threat imposed by the Yemeni migrants (11.14%) [5]. In addition to the legal migrants, a large number of unaccounted illegal migrants are found in most of the provinces. The significance of this was shown in a recent study that reported that treatment defaulters of TB are mainly illegal migrants [19].

## Transmission dynamics of TB in Saudi Arabia

To date, the published studies showed the distinct role of migrants in the transmission dynamics of TB in the country. Few recent studies have reported current TB transmission trends in the country. A study on 39 patients with multiple episodes of TB within an 18-month period showed a trend of reactivation of remote

infection eventually followed by an exogenous reinfection. The most striking finding was that 35.9% of the reinfection was caused by drug-resistant strains, including MDR-TB. This trend was most pronounced among the migrants from African countries [20].

Another study conducted on a nationwide collection of drug-resistant TB isolates showed the transmission cycle of TB in the country between the Saudi and non-Saudi patients to be highly admixed. The majority of drug-resistant strain clusters were shared between the Saudi and non-Saudi patients. There was little difference between the distribution of strain lineages in both local and immigrant groups. However, the highest ratio (59.5%) of the shared strain clusters showed the typical social mixing of the resident populations [21].

Varghese *et al.* recently reported on the transmission of TB among the autochthonous and immigrant populations of the eastern province in Saudi Arabia, which has a large population of migrants [6]. The recent transmission index in the region was 32.1%. Of particular interest was the observation that 75.8% of the strain clusters were shared between indigenous and immigrant populations, particularly immigrants from Southeast Asia (40.7%). In contrast, cross-national transmission among the immigrant groups was very limited (24.2%). This study concluded that the socio-economical characteristics of the migrant group have a distinctive and detectable impact on the diversity of strain lineages and transmission dynamics of TB in the eastern province of Saudi Arabia [6].

### Molecular epidemiology of *Mycobacterium tuberculosis* in Saudi Arabia

The Saudi Arabian resident population has a unique structure as it includes people from more than 100 countries, many from TB-endemic areas. This has a high impact on the phylogenetic composition of *M. tuberculosis*, as almost all the defined phylogenetic lineages have been identified from Saudi as well as non-Saudi patients.

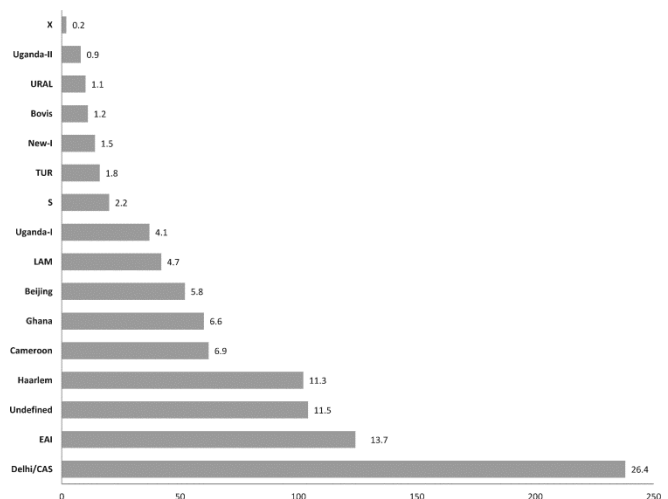
The first nationwide study on molecular epidemiology of *M. tuberculosis* was conducted on 1,505 clinical isolates collected from seven provinces of the country during 2002–2005. The genotyping results revealed 387 individual genotype patterns, a clustering rate of 86.4%, and 182 clusters containing between 2 to 130 isolates per cluster. A total of 94% of the strains matched to the spoligotype patterns in an international database. The majority of the isolates (81%) were imported strains including the following

clades: Central Asian (CAS, 22.5%), ill-defined T clade (19.5%), East African Indian (EAI, 13.5%), Haarlem (7.5%), Latin American Mediterranean (LAM, 7.2%), Beijing (4.4%), Manu (2.7%), X (0.9%), and *Mycobacterium bovis* (0.9%). In addition, two clonal complexes were identified with unique spoligotyping signatures (octal codes 70377707770371, and 67777377413771), which were specific to Saudi Arabia [21].

Recently, Al-Hajoj *et al.* conducted a study on a nationwide collection of 902 isolates and reported the impacts of demographic factors on the trend of molecular epidemiology of TB. The findings revealed the same large diversity of *M. tuberculosis*, and that some strains (TUR, S, Ghana and Uganda-I) were found to be more prevalent among elderly (> 65 years) patients. The strain cluster ratio was relatively low (12.5%) among the elderly group, whereas children (< 15 years) showed the highest (43.1%) ratio. The study finally concluded that the current population structure of *M. tuberculosis* in Saudi Arabia is highly diverse, with significant associations with demography, transmission dynamics, and origin of patients. The difference in genotype distributions among young and elderly patients reflects the ongoing change in the strain population structure in the country [22] (Figure 5).

Another retrospective analysis by Varghese *et al.* conducted on 524 isolates from the industrialized eastern province of the country showed the same large diversity of *M. tuberculosis*. This study also revealed a large diversity with 14 lineages, which were shared between autochthonous and immigrant populations [6].

**Figure 5.** Nationwide phylogenetic diversity of *Mycobacterium tuberculosis* [22]



### Phylogenetic distribution of drug-resistant *M. tuberculosis*

In 2013, Varghese *et al.*, in a study of drug-resistant isolates from a nationwide collection, found that 14 strain lineages are common among the Saudi resident population. Major lineages observed were Delhi/CAS (21.1%), EAI (11.2%), Beijing (11.2%), and main branches of the Euro-American super-lineage such as Ghana (14.9%), Haarlem (10.6%), and Cameroon (7.8%). In addition, *M. bovis* BCG (4.6%), Uganda-I (2.8%), S (2.5%), X (2.2%), New I (1.5%), and TUR (1.5%) were also observed. Interestingly, a higher representation of lineages X, S, Haarlem, and *M. bovis* BCG were observed among Saudi nationals, whereas EAI, Beijing, Delhi/CAS, and Ghana were well defined among immigrants, even in the highly admixed nature of strain clustering [21].

### Epidemiology of drug-resistant tuberculosis in Saudi Arabia

Few small-scale studies conducted in the country have reported the proportion of resistance to any first-line drugs ranging between 14% and 20%, with MDR-TB between 1% and 44% [23-29]. These studies were retrospective analyses focused on specific categories of patient populations and did not follow any standard guidelines or quality control measures. Until 2013, the true burden of drug-resistant TB was not known, as the country never conducted a representative national survey to measure levels and patterns of anti-TB drug resistance. In 2013, Al-Hajoj *et al.* reported the results of the first nationwide drug surveillance survey conducted with a representative population of nationals and immigrant patients. This was the first study in the country conducted under the guidelines of the WHO with strict quality control analysis. A nationwide annual collection of 1,904 *M. tuberculosis* isolates from all the provinces were subjected to first-line drug susceptibility testing. The results were promising; a low level (4%) of MDR-TB was found, whereas the rate of any drug resistance was found to be 23.6%. Though the MDR-TB was low in prevalence, it was strictly confined to the western region of the country and was more predominant among immigrant workers [6].

Interestingly, large discrepancies in the reporting of drug susceptibility testing of *M. tuberculosis* were reported in the country, particularly in defining MDR-TB. A recent study conducted with a nationwide collection of isolates showed discrepancies of 2.3% in defining MDR-TB between diagnostic laboratories

around the country. Nonetheless, there was also a high level of strains falsely reported as resistant (36.3%), and false susceptibility among the reports from the diagnostic laboratories was found to be 31.8%. These findings show that even though a common diagnostic technique is followed in all the laboratories, errors are still made. Moreover, the false-positive or false-negative reporting has serious consequences for patient management [30].

### Molecular characterization of drug-resistant TB

Recently, Varghese *et al.* investigated the diversity of mutations in both INH- and RIF-resistant *M. tuberculosis* isolates. High frequency of *rpoB* codon 531 mutations (67.1%) in RIF-resistant strains and *katG* codon 315 mutations (65.2%) in INH-resistant strains were reported. In addition, mutation to *inhA* position -15 conferring INH resistance and codons 516, 510, and 526 of the *rpoB* gene were also observed. Mutations responsible for INH resistance, *katG* 315, and *inhA* position -15 were predominant among the newly diagnosed cases [31]. Another recent study on a nationwide collection of 415 INH- and RIF-resistant isolates, to determine the diverse occurrence of mutations among local and migrant population, showed huge diversity of *rpoB*, *katG*, and *inhA* mutations, along with some unknown mutations. In addition, a statistically significant association between the geographical origin of the patients and the type of mutations observed were clearly evident. The autochthonous population showed a predominance of *rpoB* codon 516 and 526 mutations. However, the *inhA* promoter position -15 and -8 mutations were more prominent among immigrants [32].

### HIV and TB in Saudi Arabia

Despite the introduction of an HIV surveillance program in 1984, new incidences of the disease are increasing, particularly among Saudi nationals. The recently reported incidence rate is < 4 cases/100,000 population [33]. The screening of HIV in TB patients has been sub-optimal in the country for decades [6,34]. In contrast, recent WHO statistics show that 89% of the total TB patients in the country had been screened for HIV, which is a promising result [1].

A study conducted on data collected over 10 years showed that the incidence of TB in people living with HIV in Saudi Arabia is 30 times higher compared to the general population. However, the number of people with HIV infection is relatively small, with only 217 people with HIV registered in the decade

1997–2007, and only 16 (7.4%) with TB co-infection. Seven developed extrapulmonary disease (44%), six had pulmonary TB (37%), while three had both (19%). The incidence rate of TB was 1,354/100,000 population among the HIV-infected cohort, with an incidence rate of pulmonary TB of 762/100,000 and extrapulmonary TB of 592/100,000 [35].

In the recent nationwide TB drug surveillance survey, only 17 patients with TB/HIV co-infection (< 1% of those enrolled) were observed, and the majority (53.7%) of those enrolled had unknown HIV status [6]. The lack of association between drug resistance and HIV found in this study was therefore not surprising, as similar findings had been made previously [34]. Thus, this finding should not be considered conclusive because of the large proportion of patients with unknown HIV status [6].

Due to the unique sociocultural and religious context in Saudi Arabia and non-acceptance of individuals with HIV-related risk behaviors, a prevention program remains a challenge in the country. However, the Ministry of Health recently developed a five-year plan to reduce the death of HIV patients with TB by 50% in 2015. A long-term strategic plan is made and implemented with eight dedicated treatment facilities and diagnostic facilities in major cities. All Saudi nationals receive free treatment, and non-Saudis are usually deported to their countries if they are diagnosed to have HIV.

### **Tuberculosis control program setup in Saudi Arabia**

The activities of National TB Control Program (NTP) of Saudi Arabia are integrated into the general healthcare facilities. A central TB unit in the Preventive Medicine Directorate of the Ministry of Health directs and supervises the program by making policies, monitoring, evaluating, training, and coordinating with the different levels of the governmental health system and other sectors involved in TB control activities. TB care services are integrated in general healthcare facilities mainly because of the social stigma accompanying TB in the country. The key players in the TB treatment are the two chest hospitals (nationwide referral centers for MDR-TB management) located in the central and western provinces, and other two TB centers with outpatient clinics in the eastern and western provinces. However, identification of TB suspects is performed at all levels of healthcare services by general practitioners and specialists. Diagnosis of TB patients and prescription of treatment is only performed in

hospitals by specialists, while follow-up is undertaken in hospitals and by general practitioners in primary healthcare centers. Diagnosis of TB in the country is mainly based on sputum smear microscopy, radiography, mycobacterial culture, and histopathology. In addition, limited molecular techniques are available only in some referral laboratories.

Surveillance starts at the outpatient clinics and in primary healthcare centers by general practitioners. Patients suspected to have TB are listed in a suspect register and referred to nearby hospitals for diagnosis. An assigned coordinator in the same hospital is notified of confirmed TB patients. If there is no assigned coordinator, the infection control section is notified, which in turn notifies the district coordinator, using the adopted notification form. After notification, the district coordinator assigns the case a unique number in the TB register and informs the hospital coordinator of that number in order to label the patient's treatment card. Patients are given appointments by the treatment physicians for follow-up and smear examination. Smear microscopy results are kept in the patient's file and a copy is sent to the district coordinator to be recorded in the TB register. District coordinators submit a monthly case-based report to the central unit, including new and relapse patients, in addition to treatment outcome. Patients who default on treatment are traced and contacted by an outpatient clinic nurse and the district TB coordinator [5].

### **Emergence of non-tuberculous mycobacterial infections in Saudi Arabia**

Non-tuberculous mycobacterial (NTM) infections are another emerging threat for developing as well as developed countries, even though they are opportunistic pathogens. The escalation of NTM infections is mainly related to HIV and other immunosuppressive illness [36]. Saudi Arabia is not an exception; recent studies have shown high potential of NTM infections in the country, even in immunocompetent individuals [37].

Varghese *et al.* recently demonstrated the huge species diversity of NTM for the first time in the country. This is a very different picture from that found in the Western world, where fast-growing species such as *M. abscessus* and *M. fortuitum* are more prevalent in causing clinically relevant pulmonary and extrapulmonary infections (Figure 6). This study reported for the first time the clinical relevance of the species *M. celatum*, *M. xenopi*, *M.*

*scrofulaceum*, *M. lentiflavum*, *M. asiaticum*, and *M. simiae* in the country. In addition, 62.1% of the total study subjects were Saudi nationals. This study concluded that Saudi Arabia has an increasing magnitude of true NTM diseases [38].

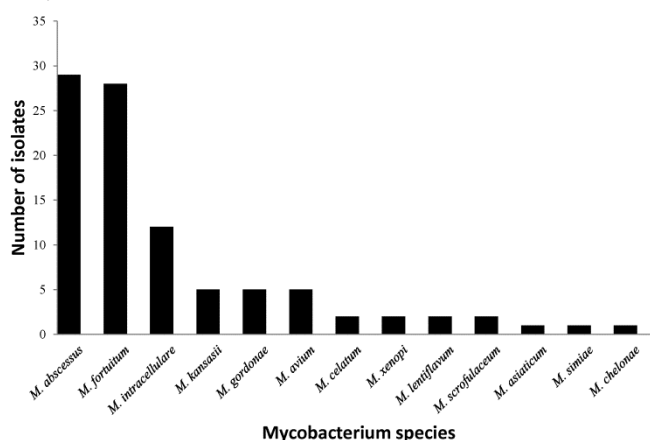
### Future milestones in controlling TB in Saudi Arabia

In Saudi Arabia, basic, applied, and clinical research, plus implementations of new policies on TB control, are still not well progressed. The majority of the TB-related publications in the country are retrospective or population-based analyses targeted at the epidemiology or clinical manifestations of the disease. Data on basic or fundamental research related to TB in Saudi Arabia is almost nil in the arena of scientific literature. However, to date, only one national drug surveillance survey and two surveys on molecular epidemiology of drug-resistant and drug-susceptible *M. tuberculosis* isolates have been conducted [21,39,40]. There is an absolute necessity for many research focal points, particularly related to the socio-economic and host-related factors of TB and the impact of various *M. tuberculosis* strains and lineages on the outcome of treatment or clinical presentations.

### Qualitative research

Non-adherence to the strategies of the WHO in performing case notification and DOTS remains high among TB patients, particularly in developing countries [1]. The reasons for such defiance have never been explored in Saudi Arabia [41]. The treatment outcome has never reached the 85% target set by the WHO, despite the implementation of DOTS in the early nineties. The treatment failure or default rate in the country was reported to be very high in previous studies, ranging from 13.23% to 30.6% [42,43]. However, recent nationwide published data is not available to assess the current status. There may be valid reasons causing such failures in the country. A recent report suggested some possibilities. These include the presence of 45%–48% of immigrant patients, the majority of whom are not well educated and unaware about the consequences of failure to complete the medications; the considerable proportion of illegal immigrants with TB who fear deportation; the lack of long-term support for most immigrants who live in the country without their families; social stigma about the disease; and fear about the lengthy hospitalization. Relevant qualitative research may be the missing link in successful TB control [41].

**Figure 6:** Nationwide species diversity of non-tuberculous mycobacteria in Saudi Arabia [38]



Therefore, immediate action is necessary to conduct a qualitative research to find the root causes of treatment non-compliance in Saudi Arabia.

### Need for a centralized advanced data registry

Currently, the Ministry of Health reports each TB case from all the provinces with a unique TB code to the central data unit. However, the information collected as part of the standard reporting procedure does not include detailed profiles of the etiologies or patients. Thus, there are no data on genetic profiling or drug resistance of the isolates. Moreover, the registry does not offer free access to clinicians or patient care professionals. To improve the management of epidemiological data and patients' profiles, a central database or registry with easy access for clinicians who are actively involved in NTP is needed urgently [44]. A central TB registry has led to better infection control practices and patient care management in developed countries. Some of the best examples of central data registry are the European Tuberculosis Surveillance Network and various registries maintained by the United Kingdom, the United States, Germany, and the Netherlands, which can be adapted by Saudi Arabia and neighboring Arab countries. The registry should include drug susceptibility profiles, genotypic profile, patient demography, treatment, and clinical history. Such a system can avoid the duplication of registration of patients under NTP when they move from one province to another. Therefore, building a new registry that can be accessed via internet by the respective users in the NTP, particularly for physicians treating patients, is essential and highly recommended.

### **Need for a central referral research laboratory facility**

The country should have a national mycobacteria referral laboratory, which can be a key player in complicated interpretations in diagnosis and research. In addition, the referral laboratory can act as a place for research, training, and standardization of new diagnostic techniques. A regular external quality assurance program can be organized by the referral laboratory to all the TB diagnostic centers to maintain uniform standards and quality. The laboratory should be well equipped with updated technologies and should support the updates on centralized data registry. The model laboratory systems of the European Reference Laboratory Network for TB (ERLN-TB) and the South Asian Association for Regional Cooperation (SAARC) countries can be adapted for the Arabian peninsula, particularly for the Gulf Cooperation Council member states [45]. However, a well-equipped reference facility along with data registries are available in most developed countries such as Canada, the United States, the United Kingdom, Denmark, Germany, and the Netherlands. On the other hand, even developing countries in Africa (*e.g.*, Uganda, Kenya, and South Africa) and Europe (*e.g.*, Georgia, Lithuania) also have a national mycobacterial reference laboratory in place [1]. Thus the need for such a laboratory in Saudi Arabia is evident.

### **Implementing modern diagnostic technologies**

New technologies should be implemented to improve case notifications, rapid diagnosis, and treatment success. Although the country has moved forward with infrastructure development for the NTP, the incomplete target achievements in case notification and treatment shows the further need for improvements. Further to the phenotypic profiling of the causative agent of TB, *M. tuberculosis*, current research is focused on a genetic profiling, which enables effective use of the modern diagnostic and treatment schemes. Molecular techniques are more rapid and sensitive and have a shorter turnaround time. Detection and treatment of drug-resistant TB requires more attention. To facilitate and improve rapid diagnosis, particularly of drug-resistant TB, modern diagnostic techniques must be adapted to all the TB diagnostic facilities. Genome-based assays are more trusted and are becoming popular in the research field. Whole-genome-based techniques have proved to be the best source of information about the causative

agents and can be used to draw up treatment regimens and to facilitate control measures.

### **Exploring host related factors of mycobacterial susceptibility**

This is the most interesting development in the field of genetic research, as various host genetic susceptibility factors towards mycobacterial diseases have been explored in recent years. As a country with the highest rate (58%) of consanguinity reported in the world and a prevalence of numerous genetic disorders, the potential of all the identified and unexplored genetic factors needs to be investigated [46,47]. Recent studies have shown that the indigenous population is affected by EPTB, NTM infections, BCG vaccine-related complications, and an upward trend of pulmonary tuberculosis [5,38]. The major assumption is that the Saudi population may have certain genetic susceptibilities towards mycobacterial diseases. Some of the factors that make people vulnerable to mycobacterial disease have already been reported from Saudi Arabia [48].

### **Conclusions**

The consistent reporting of a moderate rate of TB in the last 10 years in Saudi Arabia highlights the need to exert more attention to its control and management [5,9]. The increasing mortality rate among the Saudi population, in contrast to the steady state in the immigrants population, is a serious concern. The influx of millions of immigrant workers and pilgrims has a very high impact on TB transmission and the phylogeography of the causative agent. The poor implementation of control programs and failure to attain the WHO's global target shows the need for more vigorous strategies to be introduced and followed. The introduction and implementation of modern technologies and new research focal points are crucial, particularly analysis of population-based factors. The country urgently requires a central database or registry with phenotypic and genotypic profiles of the causative agent linked to patients' demographic data. This registry should be accessible to the treating clinicians and supportive members of the team to enable them to know the history of the patients in terms of treatment and drug resistance, and to look deeper into the genetic profile of the causative agent. This will help the clinicians to accurately diagnose the status of the disease (relapse/reactivation/reinfection) and continue with the right choice of drugs rather than administering empirical therapy. Whole-genome-based research is an



absolute necessity that focuses on host-related factors, as the population has been found to harbor several mycobacterial susceptibility genetic factors. Timely data publications will increase knowledge and introduce more research focal points. Overall, the country needs an immediate strengthening in the current control policies, research and diagnostic facilities, properly trained manpower management, and adaptation to upcoming technologies.

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