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Tuberculosis in Saudi Arabia

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1. Introduction

1.1 Demography of Saudi Arabia

Saudi Arabia is the third-largest country in the Middle East by land area, constituting the bulk of the Arabian Peninsula, and the third-largest Arab country. It is bordered by Jordan and Iraq to the north and northeast, Kuwait, Qatar and the United Arab Emirates to the east, Oman in the southeast, and Yemen in the south. It is also connected to Bahrain by the King Fahad Causeway. The Persian Gulf lies to the northeast and the Red Sea to its west. The size of Saudi Arabia is approximately 2,149,690 square kilometers (830,000 sq mi). The total population is 27,136,977 as of the April 2010 census (18,707,576 Saudi nationals and 8,429,401 non-nationals). Until the 1960s, most of the population was nomadic or semi nomadic; due to rapid economic and urban growth, more than 95% of the population is now settled. Some cities and oases have densities of more than 1,000 people per square kilometer (2,600/mile²). Saudi Arabia's population is characterized by rapid growth and a large cohort of youth.

2. National Tuberculosis Program (NTP) and Directly Observed Therapy (D.O.T.S)

In 1992, the Ministry of Health established a National Tuberculosis Control Committee to implement a control program throughout Saudi Arabia, and in 1999 the committee decided to implement D.O.T.S. The NTP in Saudi Arabia constitutes a manual, recording and reporting system, training, laboratory and X-ray services. Treatment services, drug and equipment supply is funded by the Ministry of Health. In Saudi Arabia there are several institutions providing healthcare for patients with tuberculosis; National Guard hospitals, Military hospitals, Security Forces hospitals and Ministry of Health hospitals. Patients attending private hospitals suspected of having TB are referred to government hospitals. There is no central system of record keeping, such that a patient currently receiving treatment at one institution may present to another with tuberculosis and be recorded as a new case (Al-Hajoj and Alrabiah). All institutions should report to the Ministry of Health, the body responsible for collecting data on Tuberculosis, but we believe that this is not being adhered to (Al-Hajoj and Alrabiah). Saudi Arabia's D.O.T.S success rate is comparatively well below international levels (Al-Hajoj and Alrabiah).



Fig. 1. Map of Saudi Arabia showing the total area, major cities and the borders with other countries.

3. Epidemiology of Tuberculosis world wide

According to a recent report by the World Health Organization (W.H.O); the estimated figure for the global burden of TB in 2009 reached 9.4 million cases and the total deaths hit 1.3 million among HIV-negative people and 0.38 million deaths among HIV-positive people. The report shows that most of the cases were in the South-East Asia, African and Western Pacific regions (35%, 30% and 20%, respectively).

4. Epidemiology of TB in Saudi Arabia

Tuberculosis in Saudi Arabia is still not fully controlled despite the huge efforts exerted by the government, represented by the Ministry of Health. According to the National TB Programs to eradicate the disease, TB continues to cause problems even with the implementation of D.O.T.S. It was anticipated that this program would bring the disease under control, but unfortunately the success has been limited (Al-Hajjaj 2000).

The first nationwide community-based survey of the epidemiology of tuberculosis was conducted by Al-Kassimi et al in 1990. In this study 7,721 subjects were screened in the 5 provinces. Prevalence of positive Mantoux test in non BCG vaccinated subjects and prevalence of bacillary cases on sputum culture were investigated. The authors found that

the prevalence of positive Mantoux reaction in children aged 5-14 years was 6% +/- 1.8; higher in urban areas (10%), and lower in rural areas (2%). Yet there were higher prevalence of Mantoux reaction in the urban communities in the Western province (20% +/- 8.7 urban; 1% +/- 1.9 rural). Therefore the authors concluded that Saudi Arabia is among the middle prevalence countries (al-Kassimi, Abdullah et al.). The skin test conversion rate in unvaccinated Saudi Arabian children is about 0.5% per year, lower than in sub-Saharan countries (2%) but higher than in Europe (estimated at 0.1%) (el-Kassimi, Abdullah et al.). Another epidemiological study of tuberculosis infection was carried out between January 1987 and February 1990. In this study a proportional to population size sampling method was used for the whole country. A total of 1,933 subjects were screened and a pre-designed questionnaire was used to collect details of BCG scar, age, sex, residence area, nationality, education, occupation, and a tuberculosis test was done. A number of statistically significant association was found between positive tuberculin test ($> 10\text{mm}$) and age ($p < 0.0001$), sex ($p = 0.018$), nationality ($p = 0.009$), residence area ($p = 0.05$) and occupation ($p = 0.0003$) (Bener and Abdullah). In addition. The W.H.O 2007 estimation of the incidence of TB new cases was 46/100 000 population/year, the incidence of new smear positive cases was 21/100 000 population/year and the estimated prevalence of all forms of TB cases was 65/100 000 population/year. (WHO) report <http://www.who.int/tb/country/data/download/en/index1.html>. Contrary to W. H. O. report recent data showed that the total cases for the year 2008 was 3,918 in a population of approximately 27,136,977. Therefore according to this report, the incidence of all cases was estimated at 15.8/100 000 and the incidence of smear-positive tuberculosis was 8.2/100 000. However it is believed that the incident rate of TB varies from one region to another and between citizens and expatriates. For instance in Jeddah province (Western Province) Zaman et al studied epidemiology and incidence of Mycobacterium tuberculosis and other mycobacterial species infections in a wide cross-section of population over two (2) years (1987-1989). The study showed that incidence was highest among young adults and varied between Saudi and non-Saudi patients (Zaman). Another study showed that in Jeddah (Western Province) the rate reached 64 cases per 100,000 compared with 32 per 100,000 in Riyadh (Central Province) (Al-Kassimi 1993; Qari 2002). The childhood and adolescents tuberculosis along with adult tuberculosis are on a rapid increasing phase in the country as per the available published data from the MOH statistics during the last few years (<http://www.moh.gov.sa/statistics/index.html>) with alarming rate (20%) of high prevalence of MDRTB was reported from Western region of KSA during 2001 (M Y Khan 2001).

5. Drug resistance TB in Saudi Arabia

Empirical anti-tuberculosis therapy used in Saudi Arabia usually includes three to four first line drugs including isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin. Despite the implementation of the D.O.T.S, the number of patients effectively treated in Saudi Arabia has fallen below the WHO target of 85%, (Al-Hajjaj; Alrajhi, Abdulwahab et al.; Samman, Krayem et al.). A retrospective study was conducted which included 147 patients with culture proven diagnosis of tuberculosis seen at the King Khalid National Guard Hospital, Jeddah, between June 1993 and June 1999. One hundred and twenty six patients completed treatment and treatment success was 102/147 (69.4%) and failure 45/147 (30.6%). Noncompliance and drug resistance were considered the main two factors which are significantly associated with treatment failures (Samman, Krayem et al.). Abu-Amro KK

reviewed data available for the last 10 years and he showed that the prevalence of single-drug-resistant tuberculosis ranged from 3.4% to 41% for isoniazid, 0% to 23.4% for rifampicin, 0.7% to 22.7% for streptomycin and 0% to 6.9% for ethambutol. However, the prevalence of multi drug-resistant tuberculosis (defined by WHO as resistance to two or more first-line anti tuberculosis drugs) ranged from 1.5% to 44% in different regions (Abu-Amero). Another study on 764 *M. tuberculosis* isolates obtained from 764 patients; resistance was noted in 65 (8.5%). Resistance to isoniazid was the highest, noted in 54 (7.1%); resistance to rifampicin, streptomycin and ethambutol was found to be 21 (2.7%), 29 (3.8%) and 12 (1.6%) isolates respectively. Poly resistance was noted in eight (1%) isolates and mono resistance in 38 (5%) isolates. Multi-drug-resistant *M. tuberculosis* was found in 19 (2.5%) isolates. There were 54 primary resistant isolates (7.6%), and 11 (22%) with acquired resistance. Resistance to at least one agent of the first-line anti-tuberculosis agents was 18.4%. Mono resistance to a single first-line agent was found in 10.9%, while poly resistance was noted in 7.6%. Multi-drug-resistant tuberculosis was noted in 5.7% of all isolates. Resistance to isoniazid was most commonly noted in 11% of isolates. Resistance rates to other agents were: rifampin 9.7%, streptomycin 9.1%, pyrazinamide 3.1%, and ethambutol 2.5%. Al-Hajoj et al summarized all available studies as it shown in table-1. However, the author insisted that these studies should be treated with extreme caution as many of them are old, no standardized technique, small and fragmented studies as they were carried out in a single hospital.

City	Drug resistance					MDR-TB	Reference
	RIF	INH	PZA	ETB	STR	%	
Jeddah	20.8	28.7	7.9	6.9	22.8	25	(al-Mazrou, Khoja et al.)
Riyadh	2.8	9.1	5	2.8	1.6	11.8	(Arya)
Jizan (South)	43	80	S	NA	53	44	(Ellis, al-Hajjar et al.)
Dammam	0.2	6	S	S	0.7	7	(Al-Rubaish, Madania et al.)

The above table is a summary of studies from different regions showing the percentage of drug resistance TB for single and multi anti-TB agents. It is not clear which method/s was used in each study. RIF-rifampicin, INH-isoniazid, PZA-pyrazinamide, ETB-ethambutol, STR-streptomycin, MDR-TB multi drug resistant tuberculosis.

Table 1. MDR-TB. Profile cities within the kingdom of Saudi Arabia

Recently, the King Faisal Specialist Hospital and Research Centre (KFSH&RC) TB-research unit undertook the responsibility to study drug resistance rate in the country. This study was planned with the help of W.H.O experts and in collaboration with the Ministry of Health. This study was funded by King Abdulaziz City for Science and Technology (KACST) under project # AT26-110. This study was the first of its type as it covered the whole country and in prospective mannar. The design of the study was to collect all isolates from all regional laboratories for one year. This was in concordance with W.H.O recommendation as there were no data to do cluster collection. All isolates with their epidemiological and clinical data were collected for one year starting from 01 June 2009 until

31 May 2010. A total of 2,842 were collected from 9 regions. 248 and 192 were removed from the total number as we found them to be NTM and repeated cultures respectively. Therefore the DST was carried out for 1904 isolates representing the whole country. A summary of the main findings are in table-2.

Drug	No. of resistant isolates	Rate of resistance
Any drug resistance	537	28.3%
Streptomycin	228	12%
Isoniazid	160	8.42%
Rifampicin	15	0.78%
Ethambutol	58	3.05%
Multi drug resistance	76	4%

Table 2. Summary of finding of an ongoing drug resistance surveillances.

6. Pulmonary and Extra-pulmonary Tuberculosis (EPTB)

11.7%. EPTB was reported in 1991. EPTB rates believed to be varies from one hospital to another and from one region to another (Bukhary and Alrajhi). Between 1979 and 1981 Froude and Kingston reviewed 162 cases diagnosed with EPTB from KFSH&RC. The ratio of pulmonary and extra-pulmonary TB was 1:1 during the 27-month period of the study (Froude and Kingston 1982). In 2001, extra-pulmonary TB was culture-confirmed in 2 out of every 3 cases of TB at KFSH&RC (Alrajhi, Abdulwahab et al. 2002). However, KFSH&RC is known to be a tertiary hospital and may be very selective and as a result this percentage has to be treated with extreme caution. In another hospital in Riyadh TB cases for 9 months between 1981 and 1982 was reviewed by Shanks et al. Out of 47 cases, pulmonary TB was documented in 57% of cases, and 43% were EPTB (Shanks, Khalifa et al. 1983). Mokhtar and Salman studied the details of 125 TB patients. EPTB was found in 15% of all cases identified (Mokhtar and Salman 1983). Onther study showed that EPTB accounted for 59% of all cases between 1987-1989, (Zaman 1991). However, it is worth mentioning that all the above studies may do not reflect the real picture of the incidences of EPTB. All these studies were carried out either at a tertiary hospital or in regional hospital, therefore, we recommend treating these data with extreme caution. For this reason we conducted a nation wide surveillance project to determine the rate of drug resistance in the country. In this project the whole country in a prospective manner was covered. All isolates with their epidemiological and clinical data were collected from all 9 centers where TB specimens are cultured. The total number of isolates collected was 2842. Upon classification of the type of the disease, we found that pulmonary cases form 82.4% while extra-pulmonary cases are at 17.6% (manuscript under preparation).

7. Mycobacteria other than TB

Non-tuberculous mycobacteria (NTM), also known as environmental mycobacteria or atypical mycobacteria or mycobacteria other than tuberculosis (MOTT), are mycobacteria which do not cause tuberculosis or Leprosy. As the incidence of tuberculosis fell slightly, infection by those mycobacteria became more readily recognized around the world. There is a worldwide increase in infections with non-tuberculous mycobacteria due to the emergence

of the human immunodeficiency virus (HIV)-epidemic and other factors such as immunosuppressive therapy, malnutrition, and protracted treatment with broad-spectrum antibiotics. Non-tuberculous mycobacteria (NTM) are increasingly recognized as pathogens capable of causing extra-pulmonary disease, especially in immunocompromised individuals. The pathogenicity and clinical relevance of many NTM remain poorly understood. In addition, the optimal treatment of infections caused by many NTM is undefined due to interspecies and intraspecies variabilities, drug resistance, and limited literature describing disease caused by less common organisms.

Nontuberculous mycobacteria (NTM) are common inhabitants of the environment and have been cultured from water, soil, and animal sources worldwide. Human disease is believed to be acquired from environmental exposures, and unlike tuberculosis and leprosy, there has been no evidence of animal-to-human or human-to-human transmission of NTM.

NTM mainly involves the species *M. avium complex* [MAC], *M. abscessus*, *M. Chelonae*, *M. fortuitum*, *M. scrofulaceum*, *M. marinum* and *M. kansasii* and there are many other species which is clinically relevant as a pathogen.

However, as tuberculosis declined and modern microbiological methods were developed, the importance of NTM in human disease became increasingly evident. NTM cause four distinct clinical syndromes.

1. Progressive pulmonary disease, especially in older persons caused primarily by *M. avium complex* (MAC) and *M. kansasii*.
2. Superficial lymphadenitis, especially cervical lymphadenitis, in children caused mostly by MAC, *M. scrofulaceum*, *M. malmoeense* and *M. haemophilum*.
3. Disseminated disease in severely immunocompromised patients.
4. Skin and soft tissue infection usually as a consequence of direct inoculation.

NTM are opportunistic pathogens, mostly affecting patients with preexisting pulmonary disease such as chronic obstructive pulmonary disease [COPD] or tuberculosis (TB), or those with systemic impairment of immunity. The latter group includes those with HIV infection, immunosuppressive drugs users, and leukemia patients. NTM are very common in the environment and resistant to commonly used disinfectants, so they can be present in non-sterile patient material such as sputum and contaminated medical equipment (bronchoscope washers or samples in the laboratory) and consequently cause pseudo infection (Griffith DE 2007). Without evidence of person-to-person transmission of NTM, it is proposed that humans are infected from environmental sources that may include aerosols, soil, food, water and equipment. When NTM are isolated from a usually sterile site (e.g., blood, bone marrow, lymph nodes, synovial fluid), diagnosis of true disease is generally straightforward. However, when NTM are isolated from non-sterile sources, such as sputum or bronchoalveolar lavage samples, the diagnosis is less definitive, especially when the colony numbers are low or NTM are isolated from only one cultured specimen. Therefore, it is a challenge to differentiate true NTM lung disease from contamination and colonization. Thus, finding AFB by microscopy of respiratory specimens or by culture may pose a diagnostic problem for the clinician (Society. 1997).

In recent years, non-tuberculous mycobacteria (NTM) have emerged as an important cause of opportunistic nosocomial infections, but there is little known about the isolation and identification of NTM in Saudi Arabia. Larger, multicenter regional studies or mandatory reporting will be required to better understand the changing epidemiology of NTM in patients with or without HIV infection. There are many cases of NTM infections reported from different regions of Saudi Arabia but the actual numbers of cases are still unknown. However, there are scattered studies about the prevalence of NTM in Saudi Arabia. BaHammam et al showed that NTM is about 9% (BaHammam, Kambal et al.). A nation wide population-based survey however, revealed a much lower figure of 0.004% (Alrajhi and Al-Barrak; Baharoon; Bukhary and Alrajhi; Bukhary and Alrajhi; Sanai and Bzeizi). Recent collection of more than 3000 isolates from all regions in the country revealed that NTM cases are at 10% of total cases. Further study is needed to gain insight into the nature of NTM cases. In year 2010, a new species of NTM which resembled TB in terms of clinical features and response to the treatment was identified in collaboration work between the TB research unit at king Faisal Specialist Hospital and Research Centre and international collaborators. This species was called Riyadhense.

Mycobacterium abscess also was found to cause infection in an immune competent patients (Al-Hajj et al 2012).

8. Childhood TB

Childhood TB (CHTB) is a neglected aspect of the TB epidemic, despite constituting 20% or more of the TB case-load in many countries with high TB incidence. CHTB is a significant child health problem, but is neglected because it is usually smear-negative and thus it's considered to make a relatively minor contribution to the spread of TB. Perhaps most importantly, there is a real need for prospective epidemiological studies to determine the true burden of TB among children in a wide spectrum of settings worldwide. Recent guidance has already taken a significant step in this direction by recommending NTPs record childhood TB cases by age category and clinical syndrome (WHO 2007).

As children acquire infection with *Mycobacterium tuberculosis* from adults in their environment, the epidemiology of childhood tuberculosis follows TB in adults. While global burden of childhood tuberculosis is unclear, in developing countries the annual risk of tuberculosis infection in children is 2-5 per cent. Nearly 8-20 per cent of the deaths caused by tuberculosis occur in children. It has been suggested that BCG vaccination is responsible for decrease in the occurrence of disseminated and severe disease (S.K. Kabra 2004). Crucially, a definitive microbiological diagnosis of CHTB is achieved in only a minority of cases, as young children rarely develop cavitary lung disease or expectorate sputum, and a greater proportion of cases are extra-pulmonary. Diagnosis therefore usually relies on poorly validated clinical case definitions, and both under and over-diagnosis of pediatric TB are common, with potentially tragic consequences for children who are not diagnosed (Brent, Anderson et al. 2008). Neonates have the highest risk of progression to disease, and in infancy miliary and meningeal involvement is common. Children from 5 to 10 years of age are less likely to develop disease than other age groups, and adolescent patients can present with progressive primary tuberculosis or cavitary disease (Engelbrecht, Marais et al. 2006). Most children who develop disease do so within 2-12 months of initial infection, with pulmonary TB accounting for 60-80% of all cases. The two most common forms EPTB found

in children are Lympho-hematogenous disease with multiple organ involvement and Tuberculous Meningitis [TBM]. The TBM is the most serious complication with involvement of the central nerves system and with a high mortality rate. The TBM is common in children compared to adults and its diagnosis is difficult because signs and symptoms are vague (Anna M M 2005) (Starke JR 2002). The prevalence of MDRTB in children probably reflects the level of primary drug resistance among organisms currently circulating in the community. Comprehensive studies on resistance to anti TB drugs in children are limited. It has been demonstrated that patient with MDRTB cause similar rates of infection and disease among household contacts as do the patients with drug susceptible tuberculosis.(H.Simon Schaaf 2001).

The diagnostic difficulties make to give only a little attention to children with MDRTB or children in contact with it. In controlled studies it has been shown that the rate of infection is even higher in childhood contact as compared to drug sensitive cases. The transmission of MDRTB is higher than that of sensitive TB. Treatment of MDRTB is expensive and associated with lower treatment completion and cure rates. Isoniazid is the effective drug for prophylactic therapy in children with an index case, but Rifampicin is an alternative in cases of Isoniazid resistance. In cases of MDRTB there is no proved regimen of treatment for children. The drug toxicity is much higher with second line and third line drugs regimen when treating MDRTB, multi drug regimen usually necessitating hospitalization and gradual build up of drug dosages and schedules. The treatment for MDRTB is challenging in a child and unfortunately most of the second line drugs do not have pediatric formulations (Ejaz A Khan 2002). Interruption in the transmission of *Mycobacterium tuberculosis* is one of the primary goals of TB control programs. The ability to track specific strains of *M. tuberculosis* improves the understanding of transmission and pathogenesis in a community and helps to control transmission with properly designed strategies (Kathryn DeRiemer 2004). The most common extrathoracic manifestation of TB in children is cervical lymphadenitis. A simple clinical algorithm that identified children with a persistent (longer than 4 weeks) cervical mass of 2×2cm or more, without a visible local cause or response to first-line antibiotics, showed excellent diagnostic accuracy in an area with endemic TB (Marais, Wright et al. 2006). At a global level, the WHO currently reports only smear-positive cases by age. The International Union Against TB and Lung Disease (IUATLD) currently recommends stratifying the reporting of smear-positive cases into two age categories: younger than 15 years of age and 15 years of age and older (D A Enarson 2000).

Reporting of smear-positive cases is considered a practical strategy that complements the Directly Observed Therapy (D.O.T.S) strategy. Nonetheless, an estimated 1.2 cases of smear-negative TB occur for every smear-positive case of TB. Furthermore, approximately 95 percent of cases in children younger than 12 years of age are smear-negative. Thus, the W.H.O policy of reporting only smear-positive cases by age causes a gross underestimation of the burden of TB in children (J.A. Jereb 1993). Childhood TB is a direct reflection of the incidence of adult disease within a community. A case of TB in a child usually represents primary disease transmitted from an infectious adult or adolescent and is considered a sentinel event in public health. In response to a case of childhood TB, local TB control programs ideally will conduct an investigation to identify the potential source of infection and additional cases. Due to limited resources, these investigations are not implemented in many parts of the world (Anna M M 2005). A positive culture is regarded as the 'gold

standard test' to establish a definitive diagnosis of TB in a symptomatic child. It is, however, limited by the fact that organisms may be isolated from non-diseased (asymptomatic) children shortly after primary infection, during the initial period of organism multiplication and/or occult dissemination. In addition, traditional culture methods are limited by suboptimal sensitivity, slow turnaround times, excessive cost (automated liquid broth systems) and the low bacteriological yields achieved in children with active TB. It is important to point out that adolescent children (over 10 years of age) frequently develop sputum smear-positive disease that may be diagnosed using traditional methods (B.J. Marais 2005).

As childhood tuberculosis is a sensitive marker for ongoing transmission within a community, control programs should focus on children because they are the reservoirs of future disease (Lalitkanth 2001). Most children with TB in the world are not recorded in the national surveillance systems, even though they are the ones most likely to suffer severe complications of the disease. While there are many challenges in the diagnosis and treatment of TB in children, perhaps the greatest challenge globally is to begin to identify the extent of disease in this forgotten group (Shingadia. 2004). In Saudi Arabia childhood TB is also receiving little attention. However, despite this some cases are getting reported. For instance Peritoneal tuberculosis is relatively rare compared to adults but cases are reported from two regions of Saudi Arabia in children below 12 years (Saleh 1997). Primary tuberculosis of the penis with associated bilateral inguinal lymph node enlargement and a discharging sinus is described in an infant from the Abha Region (Annobil S H 1990). Banjar et al in a controlled study of 151 cases of non cystic fibrosis bronchiectasis conducted in a tertiary care centre in Riyadh among Saudi children, showed TB form 2% of the total cases (Banjar 2007). A case of congenital transmission of tuberculosis is reported from Riyadh region as a cutaneous disease with multiple abscess and resistance to primary antibiotics (Yousef A. Al-Katawee 2007). The central nervous system tuberculosis among children is reported from different regions of the country with considerable mortality rate and diagnostic and treatment problems (Bahemuka M 1989; Al-Deeb SM 1992). In a study of causes of uveitis conducted in an ophthalmology referral centre in Riyadh, it highlighted tubercular uveitis among children during 2002 (Islam and Tabbara).

9.Factors influencing the molecular epidemiology of tuberculosis in Saudi Arabia

9.1 Hajj

Saudi Arabia is a unique place as it is the place for the two holy mosques located in Mecca and Al-Madinah. The two holy mosques are the target for the one billion Muslims from all over the world. Thus every year the two cities Mecca and Al-Madinah receive more than three million for Hajj and visits to the holy mosque in Al-Madinah. The intense congestion of Hajjies, the majority of whom are coming from high endemic places, overcrowds and the close proximity furnish the grounds for infectious diseases transmission including TB. Other factors may influence the transmission including aging pilgrims whom may suffer from underlining disease such as immunological disorders, less hygiene among some of the pilgrims and the physical efforts exerted by pilgrims. As a matter of fact several studies showed that Hajj is an opportunity for TB transmission. Wilder-Smith et al conducted a

prospective study to assess the risk of *M. tuberculosis* infection among Hajj pilgrims. He found high risk of *Mycobacterium tuberculosis* infection during the Hajj pilgrimage. In his study he showed that among 357 Singaporean pilgrims; 10% showed a substantial rise in immune response to the QuantiFERON TB assay antigens post-Hajj when compared to a pre-Hajj test (Wilder-Smith, Foo et al. 2005). Alzeer et al studied cases of pneumonia admitted to two hospitals during the 1994 pilgrimage (Hajj) season to Mecca. Sixty-four patients were enrolled in the study, of which 47 (75%) were men with a mean age of 63 years (range 21-91). Nearly all were from developing countries. Diagnosis was established in 46 patients (72%) with *Mycobacterium tuberculosis* being the commonest causative organism (20%) (Alzeer, Mashlah et al. 1998). The main finding of this study is that *Mycobacterium tuberculosis* is a common cause of pneumonia during Hajj season. As a matter of fact the variation of TB incidence among Saudi cities and in favor of Western province was attributed to Pilgrims influx.

9.2 Omra

Omra is another Islamic ritual through which individuals from all over the world target once again Mecca and Al-Madinah. The two holy mosques receive all year long hundreds of thousands whom again do come from endemic places. During the holy month of Ramadan the number of visitors to the two mosques peak again as it reaches up to three million in Mecca and may be another one million at Al-Madinah mosque. During the last 10 days of the holy month of Ramadan the majority of visitors do what is called Etekaf, during which people do not leave the grand mosques. The scene is overwhelming as a person can see individuals are sleeping and sitting next to each others. We believe such circumstances make these places fertile land for transmission of TB.

9.3 Expatriates

Saudi Arabia accommodates 8,429,401 expatriates scattered all over the country. They are in the country for work purposes. In addition considerable unknown numbers are moving around illegally and hide in farms and in houses. Unfortunately the majority of those expatriates are from endemic places; therefore they are forming a source of infection as they do not visit hospitals when they become diseased, fearing deportation after treatment.

9.4 Travelling

The Saudi national nowadays travels around the globe. Also we have a considerable number of students (more than 250 thousand including families members) studying abroad and scattered all over the world including countries where TB is high like India, Philippines and East Europe. We believe that the above mentioned factors are playing a major role in making TB spread and transmitted to the country and to outside of the country. This is supported by our recent finding of molecular epidemiology.

10. Molecular epidemiology of TB in Saudi Arabia

In 2007 we published some data on the molecular epidemiology in Saudi Arabia. A total of 1,505 clinical isolates of *M. tuberculosis*, the isolates were collected over a three year period

from seven regions of Saudi Arabia and were genotyped using spoligo and MIRU -VNTR techniques. A total of 387 individual patterns were obtained (clustering rate of 86.4%, 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. Majority of the isolates (81%) were imported strains including 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 Bovis 0.9%. In addition two clonal complexes with unique spoligotyping signatures (octal codes 703777707770371, and 467777377413771) were specific to Saudi Arabia. Another on going study is taking place in Eastern province, which is a major industrial zone of the country and thus the immigrant population is high (Al-Hajoj et al.). According to the latest census reports, 2.7 million of citizens and 0.8 million of immigrants are living in the Eastern province (Statistics Department 2010). In this study a total of 533 TB isolates were collected with their epidemiological data. All the isolates were genotyped and lineages were assigned by using the online database www.miruvntrplus.org. There were 14 lineages identified among the study groups and 24 (4.5%) cases belonged either to undefined lineage or *M. bovis*. Among the total cases, Delhi/CAS (32%) and EAI (21.3%) are dominating, followed by Ghana (9.9%) and Haarlem (9.3%). TB population of the Saudi patients showed a higher predominance of Delhi/CAS (71/33.3%), followed by EAI (32/15%) and Ghana (24/11.3%). On the other hand, the non-Saudi isolates showed the domination of Delhi/CAS (100/31%) and EAI (82/25.5%), followed by Ghana (29/9%). The total numbers of undefined lineages were 17, and *M. bovis* (7 cases) was circulating only among Saudis. Cluster analysis showed 28 clusters of 148 isolates with a size of 2-18. Major clustering was found among the lineages Delhi/CAS (7 clusters) and EAI (6 clusters).

The study showed that some clades are circulating among Saudi only, others circulating among non-Saudi, and the rest circulating among both Saudi and non-Saudi (manuscript under preparation).

11. BCG vaccination

In Saudi Arabia BCG vaccine is given to every born baby as mandatory policy trying to protect the population against TB infection. It is believed that BCG is protecting against TB infection and may protect against Miliary Tuberculosis. BCG vaccination is being debated nowadays in Saudi Arabia as whether to continue to give the vaccine, delay it or stop it all together. Three years ago King Faisal Specialist Hospital and Research Centre held a conference on "Infections in Immunocompromised host" (18-19 November 2008). In this symposium, many specialists expressed their reservations about administering tuberculosis vaccine (BCG vaccine) to newborn children. They pointed out that in some cases of pediatrics with immune deficiencies, it is very important to delay the vaccination plan until the possibility of genetic immune deficiency has been ruled out. This is due to the complication of the vaccine and the dissemination of the disease. In addition, the country lacks data regarding the efficiency of BCG vaccination. In other words, we do not know whether BCG vaccine is protecting or not. Therefore the question is can we stop giving BCG vaccine to our babies? The philosophy behind this question is that BCG vaccine may not protect against TB; otherwise, why do we have up to 4000 cases yearly (according to a recent report by the Ministry of Health) despite the fact that all our babies are vaccinated at birth? BCG vaccination may cause confusion when skin test is carried out. Interpretation of skin

test is extremely difficult in light of the fact that the protein used in skin test is shared by many species of mycobacteria. Shared protein is the main cause of the confusion (Mittrucker, Steinhoff et al.). Therefore positive skin test means i) exposure to real infection, ii) exposure to environmental mycobacterium or iii) reaction due to BCG vaccine itself. BCG vaccination causes a particular problem when it comes to diagnosing dormant TB using TST. It is for this reason that the BCG vaccine is not given in many countries such as The Netherlands, UK, and recently France; yet these countries have better control over tuberculosis when compared to many countries, including Saudi Arabia, where BCG vaccine is mandatory.

To rule out the confusion caused by BCG vaccination we either have to stop BCG vaccination all together or introduce Interferon- γ tests (interferon gamma release assays, IGRAs) as additional diagnostic tools. IGRAs are based on the ability of the *Mycobacterium tuberculosis* antigens for early secretory antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) to stimulate host production of interferon-gamma. Because these antigens are not present in nontuberculous mycobacteria or in BCG vaccine, these tests can distinguish between latent tuberculosis infection in asymptomatic patients and exposure to BCG or nontuberculous mycobacteria. The test is approved for diagnosis of latent tuberculosis and has also been used in patients with pulmonary tuberculosis (Al-Orainey; Stephan, Wolf et al.). We fully approve of the establishment of such diagnostic tools everywhere in the country. It is an expensive test at this particular stage but it is worth using, as delay in diagnosing difficult cases such as extra-pulmonary is more costly to the patients (as it might cost them their lives). In addition treating dormant tuberculosis, particularly when it comes to close contact individuals, is far cheaper than treating patients after they show full symptoms of the disease. On the other hand, it is a very bad practice to give prophylaxis to treat dormant tuberculosis based on skin test results as the test has proved its inability to distinguish real infection from exposure to environment tuberculosis or BCG vaccine. Also, giving a prophylaxis indiscriminately based on skin test gives a chance for drug resistance to develop. We believe it is the right time now to review our policy of giving BCG vaccine to our newly born babies as it is creating more confusion rather than providing protection: It causes diseases in immunocompromised patients. BCG vaccine causes confusion when it comes to interpretation of skin test results. Also, it gives false-positive and false-negative results.

12. HIV and TB in Saudi Arabia

Saudi Arabia started surveillance for HIV in 1984. Clinical suspicion, screening of contacts of HIV infected patients, routine screening of blood and organ donors, prisoners, intravenous drug users, patients with other sexually transmitted infections, expatriates pre-employment testing are among reasons for HIV testing. All cases from 1984 through 2001 were reviewed. A total of 6,046 HIV infections were diagnosed, of which 1,285 (21.3%) of cases were Saudi citizens. HIV infections among Saudi citizens gradually increased over 18 year period, and jumped from 84 to 142 cases per year. The number of cases per 100,000 populations varied widely between regions. The infection was most common in the age group 20-40 years. The modes of transmission among Saudi citizens and expatriates were heterosexual contact, blood transfusion, perinatal transmission, homosexual contact, intravenous drugs, and bisexual contact. A total of 514/1285 (40%) Saudi patients died by year 2001.

TB infection is found to be associating with HIV infection like anywhere in the world. Alrajhi et al reviewed retrospectively medical charts of 437 patients diagnosed with tuberculosis from 1995-2000 in Riyadh. He found that screening was done for 178 (41%) patients: 2 (1.1%) of these were found to be HIV positive. In Saudi Arabia, screening for HIV in tuberculosis patients remains underutilized (Omair, Al-Ghamdi et al.).

217 new adult patients joined the HIV program between 1997 and 2007. TB was diagnosed in 16 patients (7.4%), all of whom had acquired immune-deficiency syndrome at the time of TB diagnosis. Seven developed extra-pulmonary disease (44%), six had pulmonary TB (37%), while three had both (19%). The TB incidence rate was 1,354 per 100,000 among the HIV-infected cohort. The incidence rate of pulmonary TB was 762/100,000 and for extra-pulmonary TB it was 592/100,000. Among pulmonary TB with HIV infection in Saudi Arabia, TB incidence is 30 times higher than in the general population, with significant mortality despite early diagnosis, treatment and tertiary care support (Al-Mazrou, Al-Jeffri et al.; Alrajhi; Alrajhi, Halim et al.; Alrajhi, Halim et al.; Alrajhi, Nematallah et al.; Edathodu, Halim et al.; Kordy, Al-Hajjar et al.; Madani; Madani, Al-Mazrou et al.; Memish and Osoba).

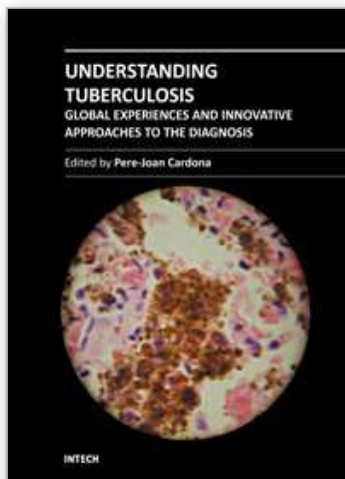
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Mycobacterium tuberculosis is a disease that is transmitted through aerosol. This is the reason why it is estimated that a third of humankind is already infected by Mycobacterium tuberculosis. The vast majority of the infected do not know about their status. Mycobacterium tuberculosis is a silent pathogen, causing no symptomatology at all during the infection. In addition, infected people cannot cause further infections. Unfortunately, an estimated 10 per cent of the infected population has the probability to develop the disease, making it very difficult to eradicate. Once in this stage, the bacilli can be transmitted to other persons and the development of clinical symptoms is very progressive. Therefore the diagnosis, especially the discrimination between infection and disease, is a real challenge. In this book, we present the experience of worldwide specialists on the diagnosis, along with its lights and shadows.

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