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عنوان البحث:

Epidemiology of Tuberculous and Drug-Resistant Challenges in Aseer Region, Saudi Arabia

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INTRODUCTION:

Each year, on March 24th, the world commemorates the "World Tuberculosis Day" when Dr. Robert Koch announced on that day in 1882 the historic discovery of *M. tuberculosis*, the causative bacillus of tuberculosis (TB). This discovery was the first step that paved the way for the diagnosis and treatment of one of the deadliest infectious diseases in the world. The goal of World TB Day is to raise public awareness about the devastating health, social, and economic consequences of TB, and to intensify efforts toward its elimination ⁽¹⁾.

Tuberculosis is a chronic infectious disease, caused by *M. tuberculosis*. It constitutes one of the leading causes of morbidity and mortality worldwide ⁽²⁾. During the 20th century, incidence, prevalence, and case fatality rates steadily fell in the developed countries. This could be attributed to prevention measures, along with good public health practices and better treatment ⁽³⁾. However, this decline was reversed afterward, and it is reported that one TB patient dies every 20 seconds somewhere in the world ⁽⁴⁾.

Ashaba et al. ⁽⁵⁾ stated that, in 2018, an estimated 10 million people fell ill with TB worldwide and over 1.5 million patients died from the disease, while an estimated 58 million lives were saved through timely diagnosis and treatment between 2000 and 2018. However, ending the TB epidemic by 2050 remains among the ambitious health targets of the sustainable development goals.

Each day, more than 4100 patients lose their lives due to TB, and almost 28,000 people fall ill with TB, although it is both preventable and curable. On

the other hand, global efforts to combat TB could save about 66 million lives since 2000. However, the COVID-19 pandemic has reversed several years of successful fight to end TB, and for the first time in over a decade, TB deaths increased in 2020 ⁽⁶⁾.

Tuberculosis remains a key public health concern in the KSA, which is at a global focal point for the influx and outflux of pilgrims, as well as the expatriates who constitute a big portion of the population. Therefore, KSA is not only more prone to the national spread but may become a hotspot for the spread of TB, especially multidrug resistant TB ⁽⁷⁾.

The WHO ⁽⁸⁾ emphasized that, in TB prevalence studies, where risk factor data are collected, special care must be taken to maintain the confidentiality of all data.

STUDY PROBLEMS:

The Epidemiological Study of Tuberculosis (TB) in Saudi Arabia Faces Several Challenges Including Issues Related to Drug-resistant TB. Here are the Key Problems:

1- Epidemiological Challenges of TB in Saudi Arabia:

- **High-risk Populations:** TB is More Common among Expatriate Workers, especially those from high-TB-burden Countries.
- **Late Diagnosis:** Many Cases are Diagnosed at an Advanced Stage, Increasing Transmission Risk.
- **Underreporting and Surveillance Gaps:** Some Cases May go Undetected, Especially among Undocumented Migrants (The Unknowns).

- **Co-infection:** TB-HIV co-infection is Rare in Saudi Arabia But Remains a Potential Concern.
- **Health Care Access:** While Health Care is Generally Advanced, Some Cases may Face Difficulties in Accessing Proper TB Care.

2- **Drug-Resistant TB Challenges:**

- **Rising Drug Resistance:** Multi-drug-Resistant TB (MDR-TB) is Increasing, Making Treatment More Complex.
- **Long Treatment Duration:** MDR-TB Requires Lengthy Treatment (Up to Two Years) With More Side Effects.
- **High Treatment Costs:** MDR-TB Drugs are Expensive and Place a Financial Burden on the Health Care System.
- **Limited Diagnostic Capacity:** While Advanced Diagnostic tools are Available in Major Hospitals, Rural Areas may have Limited Access.
- **Patient Non-Adherence:** Due to Long Treatment Courses and Side Effects, Some Patients Stop Treatment Early, Increasing Resistance Risk.

AIM OF STUDY:

This study aims to explore the epidemiology of tuberculosis among patients registered in Aseer Region, Saudi Arabia.

OBJECTIVES:

- To identify the characteristics of TB among active TB cases in Aseer Region, Saudi Arabia.
- To identify the risk factors for TB in Aseer Region, Saudi Arabia.

STUDY QUESTIONS:

Here are some study questions to guide research on the epidemiology of tuberculosis (TB) in Saudi Arabia and the challenges of drug-resistant TB:

Epidemiology of Tuberculosis in Saudi Arabia

1. What are the current TB incidence and prevalence rates in Saudi Arabia?
2. Which populations in Saudi Arabia are most at risk for TB, and why?
3. What role does migration play in TB transmission within the country?
4. How does Saudi Arabia climate and geography influence TB spread?
5. What are the main factors contributing to TB underreporting or late diagnosis?
6. How effective is the national TB surveillance and reporting system?
7. What is the impact of co-morbidities (e.g., diabetes, HIV) on TB incidence?
8. How do socioeconomic factors (e.g., housing, employment) affect TB transmission?
9. What policies exist for TB screening, particularly for expatriate workers?
10. What strategies are used for TB prevention and control in Saudi Arabia?

RESEARCH HYPOTHESIS:

Here are some potential research hypotheses for studying epidemiological tuberculosis (TB) in Saudi Arabia and the challenges of drug resistance:

Epidemiological Hypotheses:

1. Demographic Factors and TB Incidence:

H1: Immigrant populations in Saudi Arabia have a higher prevalence of tuberculosis compared to the native population due to increased exposure in high-burden countries.

2. Socioeconomic Status and TB Transmission:

H2: Lower-income individuals in Saudi Arabia are more likely to contract TB due to overcrowded living conditions and limited access to healthcare services.

3. Impact of Diabetes on TB Progression:

H3: Patients with diabetes mellitus in Saudi Arabia have a higher risk of developing active TB compared to non-diabetic individuals.

4. Effectiveness of TB Screening Programs:

H4: Routine TB screening among high-risk groups (e.g., healthcare workers, prisoners, and expatriate workers) significantly reduces the rate of undiagnosed TB cases in Saudi Arabia.

5. Seasonal Variation and TB Transmission:

H5: The incidence of TB in Saudi Arabia is higher in colder months due to increased indoor crowding and reduced ventilation.

Drug-Resistant TB Hypotheses:

6. Prevalence of Multidrug-Resistant TB (MDR-TB):

H6: The prevalence of multidrug-resistant tuberculosis (MDR-TB) is increasing in Saudi Arabia due to incomplete TB treatment and poor adherence to medication regimens.

7. Genetic Mutations and Drug Resistance:

H7: The most common genetic mutation associated with drug-resistant TB in Saudi Arabia is the *rpoB* gene mutation leading to rifampicin resistance.

8. Treatment Outcomes of Drug-Resistant TB:

H8: Patients with MDR-TB in Saudi Arabia have a lower treatment success rate compared to those with drug-sensitive TB due to prolonged treatment duration and side effects.

9. Healthcare Infrastructure and MDR-TB Management:

H9: The lack of specialized MDR-TB treatment centers in rural areas of Saudi Arabia contributes to higher rates of treatment failure and disease transmission.

10. Association of Previous TB Treatment with MDR-TB Development:

H10: Patients with a history of previous TB treatment in Saudi Arabia are more likely to develop drug-resistant TB due to incomplete or inadequate therapy in the past.

REVIEW OF LITERATURE

A) National studies

Abouzeid et al. ⁽⁹⁾ conducted their 10-year retrospective analysis of all TB cases reported in KSA to assess the trends in incidence rates by province, nationality, country of origin, and gender. Data were obtained from TB reporting forms returned to the Saudi MOH. Results showed an annual increase in the number of TB cases registered from 3,284 in 2000 to 3,964 in 2009. Non-Saudis had nearly twice the TB incidence rate compared to Saudis ($P < 0.05$). All but four provinces (Najran, Riyadh, Makkah, and Tabuk) showed decreasing trends in TB incidence rates. The highest rates were seen in the 65+ age group. In the 15–24 year age group, the incidence rate significantly increased from 15.7/100,000 in 2000 to 20.9/100,00 in 2009 ($P < 0.05$). The incidence of TB in Saudi males was higher than that of Saudi females. Conversely, for non-Saudis,

the TB incidence rates were significantly higher in females compared to males. The study concluded that despite the high investments in TB control over 15 years, TB remains an important public health problem in KSA, affecting all age groups, and different nationalities alike. The identification of the major risk factors associated with the persistently high TB rates in workers migrating to KSA is required. Moreover, proper interventions to reduce TB incidence rates are required as have been implemented by other countries.

Al-Orainey et al. ⁽¹⁰⁾ conducted their study to evaluate the trends in incidence rates of TB over the period from 1991 to 2010, and to assess the impact of the NTP on incidence trends. The study included TB surveillance data reported by the Saudi Ministry of Health. There were a total of 64,345 reported TB cases over the study period. Almost half of these (48%) were Non-Saudi. TB annual incidence rates ranged between 14/100,000 and 17/100,000. For Saudis, the rate ranged between 8.6/100,000 and 12.2/100,000. Non-Saudis had 2-3 times higher incidence. The disease trend rose over the first 10 years of the study period then it started to fall slightly. The incidence increased with age, but only people older than 45 years showed a declining trend. Regional variations were observed. Makkah and Jazan regions had the highest incidence rates. Disease trends have been rising over the last 10 years in Makkah and Central regions. The study concluded that TB control is facing some challenges in several regions of KSA and the NTP needs to evaluate and improve TB control strategies to reduce disease incidence to elimination levels.

The study of Almutairi et al. ⁽¹¹⁾ calculated the TB incidence rates in KSA from 2005 to 2012 which were stratified by nationality, gender, and administrative regions. Furthermore, laboratory capabilities were assessed by determining the proportion of laboratory-confirmed TB cases. Results showed that the overall TB incidence rates decreased from 15.80/100,000 population in 2005 (95% CI: 15.29–16.31) to 13.16/100,000 population in 2012 (95% CI: 12.74–13.58). The incidence rates were greater for males than for females from

2009 to 2012. The incidence rates of non-Saudis were approximately two times those of Saudis during the study period. Mecca had greater incidence rate during the study period compared with other regions (25.13/100,000, 95% CI: 24.7–25.56). Among non-Saudis, those from Indonesia and Yemen had the greatest proportion of TB cases (15.4% and 12.9%, respectively). Individuals aged less than 15 years comprised 14.2% of the TB cases. Employed non-Saudis had the greatest proportion of TB (32%), followed by unemployed Saudis (22.38%). The proportion of laboratory-confirmed cases of reported TB was 57% from 2005 to 2012. The study concluded that for effective prevention and control, TB screening should be implemented for non-Saudi workers at ports of entry and laboratory-screening capacity for TB should be evaluated.

In Aseer Region, KSA, Alshahrani et al. ⁽¹²⁾ conducted their case-control study to determine the lifestyle risk factors associated with patients with TB at the armed forces hospital. The study included 135 participants (67 TB patients, who were included from the hospital database between 2017 and 2018, and 67 controls who were selected from patients attending the study hospital with respiratory diseases other than TB. The results showed that the main factors associated with TB were overweight and obesity [OR: 4.40, 95% CI: 1.27-15.25 and 2.38 (1.61-9.22)], smoking [OR: 1.34, 95% CI 0.52-3.43], abnormal night sleep (<8 hours) [OR:5.03, 95% CI 1.57-16.10], blue-collar workers [OR: 2.69, 95% CI: 1.02-7.28], physical exercise <3 days/week [OR: 1.41, 95% CI: 1.21-3.47]. The study concluded that lifestyle and socioeconomic conditions are significantly associated with TB.

Alawi et al. ⁽¹³⁾ conducted their retrospective study to analyze the evolution of TB epidemiology in Saudi Arabia in the 5 years following the implementation of the end-TB Strategy. The study analyzed surveillance data of the National TB Control Program from 2015-2019. The annual incidence and the percentage of yearly changes were calculated and compared to the WHO milestones, which anticipate a 4-5% annual decline. Moreover, several other

epidemiological indicators of TB were examined. Results showed that the national TB incidence declined from 10.55/100,000 in 2015 to 8.76/100,000 in 2019, aligning with the WHO's 2019 milestone, estimated between 8.59-8.96/per 100,000. While the Makkah Region (40.3%) and Riyadh (24.6%) accounted for the majority of cases, and Jazan region consistently exhibited the highest incidence throughout the study period. Demographic features shifted toward a younger age category, male, and native dominance. There was a consistent decrease in resistance and intermediate sensitivity to all first-line anti-TB drugs, associated with a substantial decrease in both polydrug resistance (from 4.7 to 1.9%; $p < 0.001$) and multidrug resistance (4.4-2.4%; $p = 0.008$). the study concluded that TB incidence in Saudi Arabia between 2015 and 2019 has met the WHO end-TB milestones, predicting successful progress toward the 2035 goal.

B) International Studies

In the Haramaya District, Oroma Region, Eastern Ethiopia, Adane et al. ⁽¹⁴⁾ conducted their study to assess the prevalence and associated factors of TB among adult household contacts of smear positive pulmonary TB. A community based cross-sectional study design was conducted to included 454 participants following a systematic sampling method from all adult household contacts of smear positive pulmonary TB patients treated from July 2017 to December 2018. Data were collected using a pretested and structured questionnaire, and laboratory examination was processed using a fluorescent smear microscope. Results showed that the overall prevalence of pulmonary TB among adult household contacts was 7.8% (95% CI: 5.8-10.0). The risk factors for TB infection among household contacts were eating meals less than three times per day (AOR: 4.31; 95% CI: 1.61-11.55), consumption of raw milk (AOR: 4.12; 95% CI: 1.43-11.90), having family history of TB with more than one index case (AOR: 2.7; 95% CI: 1.02-6.92), living in poor ventilated houses (AOR:

4.02; 95% CI: 1.38-11.76), and living in inadequate size of living room (AOR: 3.4; 95% CI: 1.30-8.86). The study concluded that the prevalence of TB among adult household contacts of smear-positive pulmonary TB is high. Eating meals less than three times per day, drinking raw milk, living in poorly ventilated houses, and inadequate sizes of rooms were identified as contributing factors. Therefore, it has been recommended that the transmission of TB can potentially be reduced by better contact tracing and treatment strategies along with appropriate health education.

The study by Martial et al. ⁽¹⁵⁾ was conducted in four African countries based on the Global Burden of Disease Countries Study 2019 to examine the variations in the trends of TB incidence and mortality and the age-period-cohort statistical model to evaluate their risks associated with age, period, and cohort in males and females from Cameroon, Central African Republic, Chad, and the Democratic Republic of the Congo. In these four countries, TB incidence and mortality rates displayed decreasing trends in men and women; except for the males from the Democratic Republic of the Congo which recorded an almost steady pattern in the trend of TB incidence between 1990 and 2019. TB incidence and mortality rates decreased according to the overall annual percentage changes over the adjusted age category in men and women of the four countries, and Cameroon registered the highest decrease. Although TB incidence and mortality rates increased with age between 1990 and 2019, the male gender was mainly associated with the upward behaviors of TB incidence rates, and the female gender association was with the upward behaviors of TB mortality rates. Males and females aged between 15-54 and 15-49 years old were evaluated as the population at high risk of TB incidence and mortality respectively in Cameroon, Central African Republic, Chad, and Democratic Republic of the Congo. The period and cohort relative risks both declined in men and women of the four countries although there were some upward behaviors in their trends. Relatively to the period and cohort relative risks,

females and males from Cameroon recorded the most significant decrease compared to the rest of the countries. New public health approaches and policies towards young adults and adults, and a particular focus on elderlies' health and life conditions should be adopted in Cameroon, Central African Republic, Democratic Republic of the Congo, and Chad to rapidly decrease TB incidence and mortality in both genders of the four countries.

Ledesma et al. ⁽¹⁶⁾ conducted their study to assess global, regional, and national-level burdens of and trends in tuberculosis and its risk factors across five separate age groups, from 1990 to 2021, and to report on age-specific progress between 2015 and 2020. The study followed the Global Burden of Diseases, Injuries, and Risk Factors Study 2021 (GBD 2021) analytical framework to compute age-specific TB mortality and incidence estimates for 204 countries and territories (1990–2021 inclusive). The study quantified tuberculosis mortality among individuals without HIV co-infection using 22 603 site-years of vital registration data, 1718 site-years of verbal autopsy data, 825 site-years of sample-based vital registration data, 680 site-years of mortality surveillance data, and 9 site-years of minimally invasive tissue sample diagnoses data as inputs into the Cause of Death Ensemble modeling platform. Age-specific HIV and TB deaths were established with a population-attributable fraction approach. All available population-based data sources were analyzed, including prevalence surveys, annual case notifications, tuberculin surveys, and TB mortality, in the disease-model-Bayesian metaregression modeling tool to produce internally consistent age-specific estimates of TB incidence, prevalence, and mortality. Moreover, age-specific TB mortality without HIV co-infection attributable to the independent and combined effects of three risk factors (smoking, alcohol use, and diabetes) was estimated. In addition, as a secondary analysis, the study examined the potential impact of the COVID-19 pandemic on TB mortality without HIV co-infection by comparing expected TB deaths, modeled with

trends in TB deaths from 2015 to 2019 in vital registration data, with observed TB deaths in 2020 and 2021 for countries with available cause-specific mortality data. Results revealed an estimated 9.40 million (95% uncertainty interval: 8.36-10.5) TB incident cases and 1.35 million (1.23-1.52) deaths due to TB in 2021. At the global level, the all-age TB incidence rates declined by 6.26% (5.27-7.25) between 2015 and 2020 (the WHO End TB strategy evaluation period). 15 of 204 countries achieved a 20% decrease in all-age tuberculosis incidence between 2015 and 2020, eight of which were in western sub-Saharan Africa. When stratified by age, global tuberculosis incidence rates decreased by 16.5% (14.8 to 18.4) in children younger than 5 years, 16.2% (14.2-17.9) in those aged 5–14 years, 6.29% (5.05-7.70) in those aged 15–49 years, 5.72% (4.02 to 7.39) in those aged 50–69 years, and 8.48% (6.74-10.4) in those aged 70 years and older, from 2015 to 2020. Global TB deaths decreased by 11.9% (5.77-17.0) from 2015 to 2020. Seventeen countries attained a 35% reduction in deaths due to TB between 2015 and 2020, most of which were in Eastern Europe (6 countries) and Central Europe (four countries). There was variable progress by age: a 35.3% (26.7-41.7) decrease in TB deaths in children younger than 5 years, a 29.5% (25.5-34.1) decrease in those aged 5–14 years, a 15.2% (10.0-20.2) decrease in those aged 15–49 years, a 7.97% (0.472-14.1) decrease in those aged 50–69 years, and a 3.29% (–5.56 to 9.07) decrease in those aged 70 years and older. Removing the combined effects of the three attributable risk factors would have reduced the number of all-age TB deaths from 1.39 million (1.28-1.54) to one million (0.703-1.23) in 2020, representing a 36.5% (21.5-54.8) reduction in TB deaths compared to those observed in 2015. Forty-one countries were included in our analysis of the impact of the COVID-19 pandemic on TB deaths without HIV co-infection in 2020, and 20 countries were included in the analysis for 2021. In 2020, 50,900 (95% CI: 49,700-52,400) deaths were expected across all ages, compared to an observed 45,500 deaths, corresponding to 5,340 (4,070 to 6,920) fewer deaths;

in 2021, 39,600 (38,300-41,100) deaths were expected across all ages compared to an observed 39,000 deaths, corresponding to 657 (−713 to 2,180) fewer deaths. The study concluded that despite accelerated progress in reducing the global burden of TB in the past decade, the world did not attain the first interim milestones of the WHO End TB Strategy in 2020. The pace of decline has been unequal concerning age, with older adults (i.e., those aged >50 years) having the slowest progress. As countries refine their NTPs and recalibrate for achieving the 2035 targets, they could consider learning from the strategies of countries that achieved the 2020 milestones, as well as consider targeted interventions to improve outcomes in older age groups.

Lv et al. ⁽¹⁷⁾ conducted their study to provide a comprehensive epidemiological assessment of the global prevalence and burden of MDR-TB from 1990 to 2019. Estimates and 95% uncertainty intervals (UIs) for the age-standardized prevalence rate, age-standardized incidence rate, age-standardized disability-adjusted life years rate (ASR of DALYs), and age-standardized death rate of MDR-TB were obtained from the Global Burden of Disease 2019 database. The prevalence and burden of MDR-TB in 2019 were illustrated in the population and regional distribution. Temporal trends were analyzed by using Joinpoint regression analysis to calculate the annual percentage change, average annual percentage change (AAPC), and its 95% confidence interval(CI). The results showed that the estimates of the number of cases were 687,839(95% UIs: 365,512 to 1223,262), the age-standardized prevalence rate was 8.26 per 100,000 (95%UIs: 4.61 to 15.20), the ASR of DALYs were 52.38 per 100,000 (95%UIs: 22.64 to 97.60) and the age-standardized death rate were 1.36 per 100,000 (95%UIs: 0.54 to 2.59) of MDR-TB at global in 2019. Substantial burden was observed in Africa and Southeast Asia. Males exhibited a higher age-standardized prevalence rate, ASR of DALYs, and age-standardized death rate than females across most age groups, with the burden of MDR-TB increasing with age. Additionally, significant increases were

observed globally in the age-standardized incidence rate (AAPC:5.8; 95% CI: 5.4-6.1; $P<0.001$), age-standardized prevalence rate (AAPC: 5.9; 95% CI: 5.4-6.4; $P<0.001$), ASR of DALYs (AAPC: 4.6; 95% CI: 4.2-5.0; $P<0.001$) and age-standardized death rate (AAPC: 4.4; 95% CI: 4.0-4.8; $P<0.001$) of MDR-TB from 1990 to 2019. The study underscored the persistent threat of drug-resistant TB to public health. Therefore, countries and organizations worldwide must take immediate and concerted action to implement measures aimed at significantly reducing the burden of TB.

THEORETICAL FOUNDATION FOR THE STUDY:

A theoretical foundation for tuberculosis (TB) and drug resistance in Saudi Arabia should be based on key epidemiological, microbiological, and public health theories that explain the spread, persistence, and resistance mechanisms of *Mycobacterium tuberculosis* in the region. Below are some key theoretical perspectives:

1. Epidemiological Theories:

Germ Theory of Disease (Louis Pasteur & Robert Koch).

TB is caused by *Mycobacterium tuberculosis*, which spreads through airborne transmission.

Epidemiological Triad:

Agent: *M. tuberculosis* (drug-sensitive and drug-resistant strains).

Host: Individuals with varying immune responses, including those with comorbidities like diabetes, which is common in Saudi Arabia.

Environment: Overcrowded areas (e.g., labor camps, hospitals), poor ventilation, and healthcare accessibility impact TB transmission.

Social Determinants of Health Theory:

Factors such as migration, socioeconomic status, and healthcare access play a role in TB incidence and resistance.

Saudi Arabia has a high number of expatriate workers from TB-endemic countries, influencing TB epidemiology.

2. Microbiological and Genetic Theories:

Darwinian Evolution & Natural Selection

M. tuberculosis develops drug resistance due to genetic mutations in response to selective pressure from antibiotics.

Mutation and Selection Theory:

Spontaneous mutations in genes like *rpoB* (rifampin resistance), *katG* (isoniazid resistance), and *gyrA* (fluoroquinolone resistance) lead to Multi-Drug Resistant TB (MDR-TB) and Extensively Drug Resistant TB (XDR-TB).

Fitness Cost Theory:

Some drug-resistant strains have a biological fitness cost, making them less competitive than drug-sensitive strains. However, compensatory mutations can restore fitness, allowing resistant strains to persist.

3. Public Health and Policy Theories:

Health Belief Model (HBM).

Individual's perceptions of TB severity, susceptibility, and benefits of treatment influence adherence to TB therapy.

One Health Approach:

Recognizes the interconnectedness of human, animal, and environmental health in TB control, especially given the presence of zoonotic TB (*Mycobacterium bovis*).

Globalization and Disease Transmission Model:

Increased international travel and labor migration affect TB transmission and resistance in Saudi Arabia.

4. Socioeconomic and Cultural Perspectives:

Structural Violence Theory (Paul Farmer).

Economic and social inequalities (e.g., migrant workers living conditions) contribute to TB disparities.

Behavioral Change Theories:

Strategies like Directly Observed Treatment, Short course (DOTS) rely on behavioral interventions to ensure medication adherence and reduce resistance.

Conclusion:

The interplay of microbiological, epidemiological, and social factors explains TB and drug resistance trends in Saudi Arabia. A comprehensive strategy integrating these theories can help in developing better TB control programs, early detection, and effective treatment regimens.

METHODS

Study design

A case-control study design will be followed.

Study setting

This study will be conducted in Abha City, Aseer Region, Saudi Arabia.

Study population

All currently registered active TB cases at the 'Tuberculosis Control Unit', Abha Health Sector, Abha City (N=130) will constitute the study population.

Sample size determination

The minimum sample size for included active TB cases has been determined to be 98 cases using the Raosoft Sample Size Calculator website, according to the following data (Figure 1):

- Acceptable margin of error: 5%
- Confidence level: 95%
- Population size: 130
- Response distribution: 50%

 Raosoft®	
What margin of error can you accept? 5% is a common choice	5 %
What confidence level do you need? Typical choices are 90%, 95%, or 99%	95 %
What is the population size? If you don't know, use 20000	130
What is the response distribution? Leave this as 50%	50 %
Your recommended sample size is	98

Figure (1): Calculated sample size for the study group

Therefore, the study will include 100 active TB cases. In addition, age- and sex-matched (n=200) healthy control subjects will be recruited from those attending the Vaccination Unit in Al-Manhal Primary Healthcare Center, Abha City, Aseer Region, Saudi Arabia.

Inclusion criteria

Currently active TB patients registered at the 'Tuberculosis Control Unit', Abha Health Sector, Abha City, who will agree to participate in this study.

Data collection tool

A study questionnaire has been designed by the researcher (in the Arabic and English languages) will be used for interviewing participants in the study and control groups (See Annex).

The study questionnaire includes 29 questions (for all participants) about personal characteristics (e.g., age, gender, nationality, education, employment, monthly income, etc.), in addition to the current medical history (e.g., diabetes, renal diseases, HIV/AIDS), medications (e.g., immunosuppressives), family history of TB, and past history of imprisonment, travel, or pilgrimage during last year. Moreover, three questions will be directed to active TB cases about their currently received medications, duration of TB, and follow-up of their condition.

Ethical considerations

The ethical approvals will be obtained from the Institutional Review Board (IRB) at the General Directorate of Health in Aseer Region. Written informed consent will be obtained from participants. All participants will remain anonymous and data will be treated with full confidentiality.

Statistical analysis

Collected data will be analyzed using the Statistical Package for Social Sciences (IBM, SPSS, version 25). Frequencies, and percentages, will be used to describe qualitative variables while means and standard deviations will be used to describe quantitative variables. The Chi-square (χ^2) test will be used to compare the sociodemographic characteristics between the study groups. Moreover, participants' characteristics will be compared according to their demographic factors (e.g., gender, nationality, etc.) using the independent samples t-test or ANOVA test. Binary logistic regression will be applied to identify risk factors for TB. P-values <0.05 will be considered statistically significant.

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ANNEX

Study Questionnaire

هذا استبيان لغرض دراسة بحثية طبية - نأمل منك تعبئة الاستبانة علما بأن مشاركتك
اختيارية

نأمل من كل المشاركين الإجابة على الأسئلة التالية:

١- العمر (بالسنة) :

1- Age by years:..... years .

٢- الجنسية :

2- Nationality:.....

٣- النوع:

- ذكر
- أنثى

3- Gender:

- Male
- Female

٤- الوزن (كجم) :

4- Weight (KGM):.....

٥- الطول (سم) :

5- Height (CM):.....

٦- الحالة الوظيفية:

- لا يعمل
- يعمل

6- JOB:

- UNEMPLOYED
- EMPLOYED

٧- المهنة :

7- occupation:.....

٨- المستوى التعليمي:

- غير متعلم
- تعليم ابتدائي
- تعليم متوسط
- تعليم ثانوي
- تعليم جامعي

8- Education level

- Illiterate.
- Primary school.
- Intermediate school
- Secondary school
- University level

٩- السكن:

- عمراني حديث.
- نائي بعيد عن العمران.

9- Residency:

- Urban
- Rural

١٠- الدخل الشهري:

- أقل من ٥٠٠٠ الاف ريال
- ٥٠٠٠ الى ١٠٠٠٠ الاف ريال
- أعلى من ١٠٠٠٠ ريال

10- Monthly Income

- Less than 5000 SAR.
- 5000 to 10000 SAR .
- More than 10000 SAR.

١١- مستوى السكن:

- طابق علوي
- دور أرضي
- بدروم (تحت الأرضي)

11- Housing level:

- first floor or higher
- Ground level
- Underground

١٢- نوع السكن:

-شقة

-فيلا

12- House type:

-Apartment

-Villa

١٣- السكن:

-ملك

-إيجار

:13- House

- ownership

-rented

١٤- عدد غرف النوم في المنزل:

14- number of bedrooms in house:

١٥- عدد النوافذ في غرفة النوم:

15- number of windows In your bedroom:

١٦- عدد الاشخاص في مسكنك:

16- number of persons living together in your house:.....

١٧- هل تتوفر لك وتأكّل وجباتك اليومية الرئيسية:

- دائما

- أحيانا

- لا

:17- you can have and you can eat your daily main meals

-always .

-sometimes.

-never.

١٨- هل تم اعتقالك/حبسك لمدة تزيد عن شهر:

18- have you been ever in prison:

١٩- هل تطعمت ضد الدرن:

- نعم
- لا

19- Have you received your vaccine for TB (BCG):

- yes
- no

٢٠- هل أصيب أحد أفراد العائلة بالدرن:

- نعم
- لا

:20- Someone of your family diagnosed with TB

- yes
- no

٢١- هل أنت مدخن:

- نعم (سجائر – شيشة – أخرى)
- لا

21- ARE YOU SMOKER:

- yes (ciggerates- shisha – others)
- no

٢٢- هل انت مصاب بمرض السكري:

- نعم
- لا

:22- are you Diabetic

- yes
- no

:٢٤- هل انت مصاب بامراض الكلى المزمنة:

- نعم
- لا

:24- are you a chronic Renal disease patient

- yes
- no

٢٥- هل انت مصاب بامراض صدرية المزمنة:

- نعم
- لا

:25- are you a chronic respiratory disease patient

-yes

-no

٢٦- هل انت مصاب بالسرطان:

- نعم

- لا

:26- are you a Cancer Patient

-yes

-no

٢٧- ماهي الادوية التي تتناولها حاليا:

الدواء	نعم	لا	لا أدري
كورتيزون			
مثبطات المناعة			
تناول الكحوليات			
المخدرات			

27- if you already take medication kindly, answer the following:

Medication	yes	no	I don't know
Cortisone			
immunosuppressant			
Alcohol			
Drugs			

٢٨- هل سبق لك السفر خارج المملكة العربية السعودية خلال العام المنصرم:

- نعم

- لا

:28- do you travel outside Saudi Arabia a year ago

-yes

-no

٢٩- هل قمت بالذهاب خلال العام المنصرم الى مكة لتأدية الحج أو العمرة:

- نعم

- لا

29- have you traveled to mecca last year for omrah or pilgrims:

-yes

-no

نأمل من مرضى الدرن الإجابة على الأسئلة التالية:

١ - ماهي الادوية التي تتناولها حاليا لعلاج مرض الدرن (اذكر كل الأدوية):

الدواء	الجرعة	مدة تناول الدواء (شهر)

1- what are the anti-TB medications that you currently receive (please mention all medications):

Medication	Dose	Duration of treatment (months)

٢ - تاريخ التشخيص بالإصابة بمرض الدرن:

2- Date of diagnosis of TB:

٣ - هل تم تشخيصك مرة أخرى بعد العلاج:

- نعم
- لا

3- Have you been diagnosed after received complete treatment:

-yes

-no