

Surveillance of one-year pulmonary tuberculosis cases at Al Taif province using different diagnostic tools

Anas S. Dablood

Assistant Professor, Department of Public Health, Health Sciences College at Al-Leith, Umm Al-Qura University, Saudi Arabia.

Asdablood@uqu.edu.sa

Abstract: A longitudinal descriptive study was performed for the surveillance of pulmonary tuberculosis (TB) cases registered daily within one year at health centers of Al Taif province, Saudi Arabia, using different diagnostic tools. To determine the epidemiology of TB and the performance of diagnostic methods used to confirm cases among outpatient admissions, an initiative for effective control. Physicians screened patients for suspected TB cases (n=7153) and were subjected to one of numerous laboratory tests for confirmation. Positive TB diagnoses were considered confirmed cases (10.3%, n=744). Proportions revealed by the various tests are: direct smear (DS; 10.9%, n=3234), culture on Lowenstein-Jensen (LJ; 7.2%, n=1137), Mycobacteria growth indicator tube (MGIT; 10.3%, n=1512), direct and cultured sputum PCR (10.3%, n=1237) and (45.5%, n=33), respectively. The present screening studies concluded that sophisticated diagnostic tools, such as cultured TB PCR displayed highly sensitive test outcome, indicating that sputum culturing eliminated the obstacles of paucibacillary which accounted for low TB confirmed rate, and in combination with PCR amplification, generated a sensitivity and specificity profile with a high percentage of positive TB detection. Thus, the technique presents a useful tool for screening both early-stage and latency to improve effectiveness of TB control.

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1. Introduction

Tuberculosis (TB) is a Mycobacterium disease-causing infection (Dunn JJ et al., 2016), (Pai M et al., 2016). The organism is a non-motile, non-spore-forming, obligate aerobe, acid-fast bacillus. In case of pulmonary TB, the disease is transmitted by droplet infection, with the active disease state, characterized by various clinical features, including chronic cough, sputum production, appetite loss, weight loss, fever, night sweats, and hemoptysis (Zumla A et al., 2013). However, a latent form of the disease exists during which a patient with TB infection does not feel sick, shows no symptoms or spread the disease, and the only sign of the infection is a demonstration of positive reaction to the tuberculin skin test or TB blood test (CDCP., 2016).

Although TB is no longer considered a public health problem in developed countries, it is more prevalent in developing countries (Parsons LM et al., 2011), (Chadha VK., 2009) ranking as one of the top 10 causes of death and the leading infectious disease-causing mortality worldwide (WHO Global TB report 2018), with catastrophic costs (Prasanna T et al., 2018). According to WHO recent report, TB infection led to an estimated 1.3 million deaths (range, 1.2–1.4 million) among non-HIV individuals and an additional 300,000 deaths (range, 266,000–335,000) from TB among HIV-positive people. The global estimate is that a total of 10.0 million people (range, 9.0–11.1

million) developed TB in 2017 (WHO Global TB report, 2018), which have been attributed to lack of effective control tools (Ahmad NMR et al., 2018) and poverty-related socioeconomic factors (Ahmad NMR et al., 2018), (Dim CC., 2013) and thus, calls for immediate action to accelerate efforts towards the goal of combating this epidemic disease.

At present, the spread of the disease, its prevention, diagnosis, treatment, and the existence of resistant strains have become a major global burden. Alarmingly, statistics have shown that approximately 1.7 billion people, comprising 23% of the world's population have latent TB infection, with a risk of developing active TB disease anytime in the course of their lives (Houben RM, 2016).

Further, drug-resistant TB is a persistent public health crisis. The best 2017 global estimate was 558 000 people (range, 483 000–639 000) who developed rifampicin-resistant TB (RR-TB) (WHO Global TB report., 2018) and 8% of isoniazid-resistant (WHO Global TB report., 2017) cases which have contributed to the threat of global TB control. According to WHO report, three countries account for approximately half of the global cases of multidrug-resistance (MDR) or combined rifampicin and isoniazid resistance RR/IR-TB, which are as follows: India (24%), China (13%), and the Russian Federation (10%).

Early disease diagnosis and prompt initiation of treatment are essential for an effective TB control program. Delay in the diagnosis would undoubtedly worsen the disease management, increase the risk of death, and enhance TB transmission in a community where an active form of the disease persists, thereby, intensifying prevalence.

The severity of national TB epidemics varied widely among countries and considered a public health burden in Saudi Arabia (Al Ammari M et al., 2018). Despite numerous prevention and control measures being implemented throughout the country, such as the National TB Control Program (NTP) initiatives, which includes various activities such as policy making, monitoring, evaluation, training, and coordination with other sectors involved in TB control activities (Abouzeid MS et al., 2012), due to the composition of the population in Saudi Arabia and the country's influence by immigration and mass gatherings, mainly, during Hajj season (Al-Hajj S et al., 2013), the magnitude of the epidemiological profile of TB is apparently overwhelming. The prevalence rates range from 8.5% in Riyadh to 23.1% in Hail for Saudis. Moreover, 38% of non-Saudis in the Makkah region are affected by the disease (Al Watban AZ et al., 2014).

We predict early detection among individuals to know who has counteracted the disease to be the critical approach for preventive measures, as treatment and prevention of further transmission relies solely on knowing who is harboring the disease, whether an active or latent form. TB could be detected using several tools, including: Direct Smear method, in which smears are stained with Ziehl-Neelsen (ZN) stain and visualized under a light microscope for TB-positivity (Agarwal A et al., 2016), MGIT culture which is a serological test gives less false positive results (Agarwal A et al., 2016) and culture on Lowenstein-Jensen (LJ). The use of PCR has also been evaluated extensively in adults with pulmonary TB using sputum as the test material (Lodha R et al., 2004).

Our study sought to determine the number of pulmonary symptomatic disease cases reported during one year in health care facilities in the Al Taif province and to investigate which proportion was confirmed as TB to aid our control initiative processes. The type of tests employed in the diagnoses was also of importance to us to deduce which method presented as most sensitive, and thus, would be critical for utilization as a tool for early stage and latent TB diagnosis.

2. Material and Methods

Study design and setting

This research was a descriptive longitudinal study, carried out for one-year period (November 2017-October 2018) at Al Taif province, targeting all suspected pulmonary TB cases diagnosed at primary healthcare centers and hospitals of the region and referred to Al Taif Central TB laboratory. Al Taif province is located in Makkah region and populated by Saudi natives and non-Saudi people with worldwide countries of origin. The health services in the province are delivered via the public and private health sectors.

Case definition

Two categories of patients (n=7153) were considered for case definition: 1) suspected cases (n=6409) in which patients were suffering from the classical signs and symptoms of pulmonary TB, including a chronic cough, low-grade fever, pneumonia, appetite loss, and weight loss; 2) confirmed TB cases (744), determined by using one of different TB diagnostic tools, namely direct smear (DS), culture on Lowenstein-Jensen (LJ), mycobacteria growth indicator tube (MGIT), Direct sputum PCR, and cultured sputum PCR.

Data collection procedures

Although the surveillance system includes several qualitative and quantitative data, in this study, our emphasis was on the number of cases registered daily in the entire Al Taif hospitals in the region. Physicians at Al Taif healthcare facilities sort out all suspected clinical TB cases and were subjected to one of the numerous laboratory tests mentioned above, using early morning sputum or gastric lavage from a patient who had difficulty in producing sputum. Patients with positive TB test result were considered confirmed cases.

Data analysis

Data collection forms were scanned into a Microsoft Access database (Microsoft, Redmond, WA, USA) of the registry was imported into SAS version 9.2, for characterization of the study population into confirmed TB and non-confirmed cases. The confirmed cases were further classified according to the type of diagnostic method utilized to reveal TB positivity. The proportion of confirmed cases relative to the total number of cases in each assay group was evaluated as percentage for comparison between groups.

3. Results

Our present findings show that the overall proportion of confirmed cases of pulmonary TB in Al Taif province during a year was 10.3%, n=7153 (Table 1). The study revealed that when this total number of cases were subjected to various methods for TB validation, the proportion of confirmed cases using direct smear (DS) was 10.9% (n=3234), culture

on Lowenstein-Jensen (LJ) was 7.2% (n=1137), and mycobacteria growth indicator tube (MGIT) was 10.3% (n=1512), as shown in (Table 2). Validation of TB using molecular techniques such as direct sputum and cultured sputum PCR displayed 10.3% (n=1237) and 45.5% (n=33), respectively (Table 3). The overall comparison of the different test methods for TB confirmation demonstrated that the cultured sputum PCR method is highly sensitive, showing TB positivity of 45.5%, compared to the other test

methods which revealed positivity ranging only between 7.2-10.9% (Table 4).

Table 1. Proportion of overall confirmed tuberculosis cases of pulmonary tuberculosis in Al Taif province within a year.

TB Status	n	%
Total # Cases	7153	100.0
Confirmed	744	10.3
Not confirmed	6409	89.7

Table 2. Proportion of confirmed tuberculosis cases in Saudi Al Taif province within a year using conventional microscopy and culture methods.

Confirmation	Direct Smear (DS)		Lowenstein-Jensen (LJ)		Mycobacteria Growth Indicator Tube (MGIT)	
Total	n = 3234	100.0%	n = 1137	100.0%	n = 1512	100.0%
+ve	354	10.9%	82	7.2%	156	10.3%
-ve	2880	89.1%	1055	92.8%	1356	89.7%

Table 3. Proportion of confirmed tuberculosis cases in Al Taif province within a year using blood direct and cultured tuberculosis PCR methods.

Confirmation	Sputum Direct PCR		Cultured Sputum PCR	
Total	n = 1237	100.0%	n = 33	100.0%
+ve	127	10.3%	15	45.5%
-ve	1110	89.7%	18	54.5%

Table 4. Comparison of the PCR findings with conventional tuberculosis detection techniques.

TB Test Methods	n	+ve (%)	-ve (%)
Sputum Direct PCR	1237	10.3	89.7
Cultured Sputum PCR	33	45.5	54.5
Direct Smear (DS)	3234	10.9	89.1
Lowenstein-Jensen (LJ)	1137	7.2	92.8
Mycobacteria Growth Indicator Tube (MGIT)	1512	10.3	89.7

4. Discussions

TB remains a paramount global public health concern and has been estimated to rank about one-third of the world's population (Matteelli A et al., 2018), (Saramba I et al., 2016). Available data on TB cases and TB-related mortality are lacking in most developing countries. Despite an enhancement of the routine vaccination process against this infectious disease in these countries, its prevalence is still at a disturbing rate. Diagnosis of TB remains challenging even with the current advanced technologies, possibly due, in part, to the paucibacillary nature at the early stages of the disease (Fauci AS et al., 2018). Unfavorably, in developing countries, the emphasis is laid on passive case finding which is based on diagnosing infectious cases like TB mainly through direct microscopy of sputum specimens obtained from outpatient admissions (Mhimbira FA et al., 2017) This strategy emphasized by the National TB (NTB) Control Programs is, however, impacted by factors such as patient motivation, health professional's perception of TB suspicion during diagnosis, the type

of test ordered, its sensitivity and specificity, and whether the duration of the test result is likely to delay diagnosis and treatment initiation (Christian CS et al., 2018).

Although previous reports have shown that DNA extraction from blood samples prior to PCR amplification in genetic diagnoses is tedious and labor-intensive and has the limitations of sample contamination with foreign DNA, including that from preceding samples (Singh I et al., 2017), molecular tools like Xpert MTB/RIF, cartridge-based nucleic acid amplification test which simultaneously detects TB and antibiotic sensitivity rapidly, hence, has advanced the confirmation of cases and the determination of antimicrobial resistance in a timely manner (Rice JP et al., 2017). However, in most developing countries, decades-old technologies remain the standard procedures. Clinical diagnosis lacks standardization, and traditional and molecular microbiologic methods lack sensitivity. Immunodiagnostic tests improve sensitivity, but unable to distinguish TB disease from latent infection,

in some instances, lack specificity, making diagnosis often impossible to confirm (Dunn JJ et al., 2016). Accordingly, the battle against TB still, primarily, faces a diagnostic challenge.

This study is one of the contributions to minimize the problems associated with TB spread through situation analysis in the Al Taif province, which has unveiled that among all clinically suspected cases, only 10.3% were confirmed using different diagnostic tools. Although this finding does reveal the total number of TB cases among the population in the province, obtaining 734 (10.3%) confirmed new cases in the course of 12 months suggest that TB is a public health problem in this province. In 2014, a study conducted on TB prevalence in Saudi Arabia reported between 18.7/100,000 and 25/100,000 confirmed cases in Jazan and Makkah, respectively, while the incidences of the disease in Hail and Al Baha were 4.0% and 4.4%, respectively (Abouzeid MS et al., 2012). Al Ammari and coworkers found a total of 2098 confirmed TB cases recorded in the Saudi Arabia National TB Control and Prevention Program (NTCPP) registry of which 4.4% were multidrug-resistant and reported that TB is a principal public health concern in the country's health system (Al Ammari M et al., 2018). One reason for this expanded TB rate in Saudi Arabia is the substantial labor force from high TB endemic countries (Abouzeid MS et al., 2012). Out of 157 TB patients admitted to King Abdul Aziz University Hospital, Jeddah, Saudi Arabia (from July 1999 to July 2001), there were 36% Saudis and as many as 64% non-Saudis (Qari FA., 2002). Similarly, a TB study carried out in 2012 in the country found that non-Saudis had nearly twice the incidence rate of TB, compared to Saudi natives (Abouzeid MS et al., 2012).

In this study the outcomes of most of the diagnostic methods utilized in TB detection were yielded similar rates (7.2-10.9%), except for the cultured sputum PCR test which generated a high rate of positivity (45.5%). The direct PCR method demonstrated fairly good outcome, giving 10.3% TB cases and considering that this technique is rapid and has been shown to occur at low contamination risk, with a minimum lag period, it could serve as a good diagnostic tool (Eddabra R et al., 2018). The cultured sputum PCR method, however, yielded as high as 45.5% TB positivity, consistent with Kabir and coworkers finding which detected 45 additional patients suffering from TB, undetected with the conventional tests in Dhaka hospital in Bangladesh (Kabir S et al., 2018). Since only 33 suspected TB cases were determined using in this study with this technique, the need to examine the sensitivity of this latter test on a large scale is of paramount importance

in the selection of the most suitable laboratory test method to confirm TB cases.

Utilizing cultured patient sputum for AMPLICOR PCR system (Kivihya-Ndugga L et al., 2004) and employing the IS6110 primer (Kabir S et al., 2018) identifies specifically mycobacterial DNA and has been shown to be a specific, rapid, and robust method for the pulmonary TB diagnosis. Unfortunately, our study revealed that the least number of patients were subjected to this most sensitive TB detection technique, despite its suitability as a laboratory detection tool for confirmation of TB cases, in particular, at early and latent stages, when many test methods lack the sensitivity to reveal positive results. We envisaged that cost-effectiveness might have played a role in the technique being utilized sparingly. Thus, reinforcing this method in high TB-burden environments would require cost-effectiveness analysis to compare relative costs and outcomes and operational research involving this application for an evidence-based decision to be made.

Identifying and treating all latent TB cases seems impractical as the disease is more prominent in countries with limited healthcare resources and the potential chemotherapy-associated side-effects. Nevertheless, it is vital to screen the public with highly sensitive tools to embark on taking the necessary measures to reduce delay both in diagnosis and initiation of treatment for efficiency of TB control programs.

The strength of our research is that it demonstrated how screening a large population of >7000 suspected outpatient cases yielded only 10.3% confirmation, possibly due to the lack of sensitivity utilized for most of the diagnostic tests. Additionally, this study confirmed the efficiency of cultured sputum PCR in TB diagnosis, given that this technique is sensitive, produces relatively rapid results, and devoid of contamination. Our study, however, does not preclude limitations: First, we were unable to gather data on patients' nationality to enable classification of Saudi and non-Saudi TB cases in order to determine the contribution of migrants to the Saudi TB statistics. Second, comorbid associations such as HIV positivity, diabetes, severe kidney disease, cancers, and age with the confirmed TB cases are yet to be investigated.

5. Conclusion

Planning strategies that would efficiently lessen TB burden and mortality are critical in developing countries. Our study demonstrated that the overall proportion of confirmed TB cases using different diagnostic tools was 10.3% among the suspected cases. This low rate outcome of TB positivity might be primarily due to the lack of sensitivity of some of

the diagnostic tests performed. Unfortunately, only 33 of patient samples were subjected to what seem to be the most sensitive determined assay, the cultured sputum PCR diagnostic method, which would ultimately lessen the delay in diagnosis and subsequent reduction of infectious cases to render a TB control program effective. Hence efforts should be oriented towards employing highly sensitive diagnostic tests to benefit detection not only of active TB cases but also of very early stages and latent cases in a population, rather than advancing only the effectiveness of treatment.

This screening study concluded that undiagnosed TB is the impediment necessary to overcome besides initiatives proposed for treatment management and preventive efforts in Saudi Arabia and other developing countries.

Corresponding Author:

Assistant Professor Dr. Anas S. Dablood
Department of Public Health
Health Sciences College at Al-Leith
Umm Al-Qura University
Saudi Arabia.
Telephone: 966-555-538605
E-mail: Asdablood@uqu.edu.sa

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