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Empirical Review of the Role of Social Determinants in Treatment Outcomes in Drug-Resistant Tuberculosis Patients

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Abstract

Background: *Globally, success rate recorded for the treatment of drug-resistant TB remains low. About half of all patients with TB, often, do not complete their treatment schedule with consequent prolonged infectivity, drug resistance, relapse and death. Social determinants of health among several factors have been implicated as responsible for poor treatment outcomes.*

Objective: *This paper reviewed published empirical studies related to drug-resistant TB treatment outcomes and examined social factors that may explain the dynamics involved in treatment failures that are likely to be responsible for poor treatment outcomes among DR-TB patients.*

Methodology: *A review of empirical studies published in the available databases was conducted through a systematic search of articles indexed in Pub Med, Google Scholar and EMBASE databases. Pooled estimates of treatment success were computed and factors responsible were reported.*

Results: *The review revealed that DR-TB treatment success rate varied from between 34.5% to 78.4%. A total of 252 articles were identified through electronic search, 52 were duplicated while 16 were eligible and included in the review. Mainly, resistance to second line drugs, co-morbid conditions such as HIV, Diabetes Mellitus, male sex, older age, being underweight, positive sputum smear, presence of cavities in chest X-ray, longer duration of treatment, non-adherence, previous treatment, were frequently identified factors associated with poor treatment outcome in MDR-TB patients.*

Conclusion: *There was a dearth of studies involving social determinants in explaining the dynamics of poor treatment outcomes among DR-TB patients.*

Keywords: *Drug-resistance, Treatment Outcomes, Tuberculosis, Social determinants.*

Introduction

Global and regional burden of DR-TB disease

The age-old battle against infectious disease by mankind since the early centuries is not yet over. Emerging and re-emerging diseases such as tuberculosis continue to plague the very existence of man. Tuberculosis is currently the leading cause of death from an infectious disease worldwide and has now exceeded HIV/AIDS and malaria in this regard. All the gains made in the battle against Tuberculosis over these centuries have been lost within a few decades following the emergence of Human Immune Deficiency Virus Pandemic. This is further compounded by the re-emergence of drug resistant Tuberculosis.

Drug-resistant TB continues to be a public health challenge and remains a global health care concern that undermines recent successes recorded in the tuberculosis control initiatives (Gandhi *et al.*, 2010). The increasing proportion of multi-drug and extensive drug resistant TB has dramatically complicated diagnosis, treatment and prevention efforts leading to higher mortality rates among this category of patients. Globally, it was estimated in 2017 that 230 000 infected people died as a result of MDR/RR-TB. This is consistent with estimates obtained in 2016. Worldwide in 2018, there were about half a million new cases of TB that was reported to be resistant to rifampicin (RR-TB), the most effective first-line drug, and of these, 78% had multidrug-resistant TB (MDR-

TB). Among these cases of MDR-TB notified, 6.2% were estimated to have extensively drug-resistant TB (XDR-TB). Globally in 2018, it was estimated that 3.4% of new TB cases and 18% of previously treated cases had MDR/RR-TB with the highest proportion occurring in countries of the former Soviet Union (Global TB report, 2019).

Nigeria is the most populous country in Africa with an estimated total population of 201,929,719 (World Population Prospects UN, 2019). The public health burden posed by TB is becoming increasingly important as the country's HIV/AIDS epidemic unfolds. According to the World Health Organization, Nigeria is among the top ten countries globally and ranked 6th in the world, accounting for 80% of new TB cases and 80% of the global TB gap in case finding (WHO Global TB report, 2019).

Tuberculosis is a serious public health problem in Nigeria with a projected 429,000 new cases of TB occurring annually and in 2018 the prevalence was equivalent to 219 per 100,000 populations. Of this proportion, the WHO also estimates that the proportion of patients with MDR/RR-TB is 4.3% among new TB cases and 15% among previously treated TB cases in Nigeria. Nationwide in 2018, out of the projected annual incidence of TB, only 24% (106,533) of the total burden of the disease was notified in the country (WHO Global TB report, 2019) while there were an estimated 157,000 deaths among projected incidence TB cases.

Current estimates by the World Health Organisation show that there were 24,000 cases of drug resistant TB in Nigeria in 2018 of which less than 1800 were diagnosed and put on treatment. Though, effective treatment options now exist, three out of every four people with drug resistant TB go undiagnosed and untreated with every untreated individual is the potential to infect up to 15 additional people with the disease within a year (Economist Intelligence Unit Report, 2019).

Theoretical and conceptual clarification of problem dynamics

TB is an airborne disease caused by pathogenic, rod-like bacteria known as *Mycobacterium tuberculosis.* The disease spreads from person-to-person through the air by inhalation of aerosol droplet nuclei expelled by infectious hosts and mostly affects the lungs. However, it may affect other parts of the body including the brains, kidneys and the spine (Butler & Carr, 2013). Following close contact with an infectious case, 30–50 % of exposed individuals acquire latent TB infection (LTBI).

About one-quarter (1.7 billion) of the world's population has latent TB, which means people have been infected with TB bacteria but are not ill with the disease and cannot transmit the disease. For others, after the initial exposure to the infective agent, a state of active TB infection may occur immediately. However, in most of these major cases, the initial infection remains clinically silent and microbiologically latent. Records show that approximately 10 % of the infected individuals with the disease progresses to active TB during their lifetime and 5 % in the first two years (Bloom *et al.,* 2017). Therefore, preventing patients with LTBI from developing active disease is an important step towards breaking the cycle of transmission and decreasing the overall burden of TB worldwide (Millet *et al.*, 2013).

Tuberculosis is a poverty-related disease which is known to disproportionately affect the poorest, the most marginalized and vulnerable population groups wherever it occurs. This is majorly because improving access to diagnosis and high-quality healthcare, which are the basic requirements in the fight against TB, are often difficult to attain in these persons in their environment (Sulis *et al.*, 2014). Also, unhealthy household environment and working conditions are known to strongly contribute to the increased risk of TB infection and disease. It is also known that people with severe malnutrition or low immunity have a much higher risk of falling ill with TB (WHO TB Fact sheet, 2018). Similarly, it is estimated that smokers have approximately twice the risk of TB infection and active TB. It was found that the risk of poor TB treatment outcome was 70% greater in smokers compared to non-smokers (Gegia*et al.,* 2015). The control and treatment of TB should therefore be of utmost importance in the light of the above. Since TB involves the spread of *mycobacterium tuberculosis* from person-to-person through the air by inhalation of aerosol droplet nuclei expelled by infectious hosts and mostly affects the lungs, TB treatment aims to cure TB patients, prevent deaths from TB and to stop transmission of *mycobacterium tuberculosis* from the infected to the host community.

The aim of TB control is to break the cycle of transmission either by interrupting human transmission of infection or by protecting individuals against infection/disease. There are various levels of intervention along the natural history of TB, including early diagnosis of infectious TB cases, rapid and effective delivery of anti-TB treatment and prevention of disease through vaccination and preventive therapy (Jochem & Walley 1999). Without adequate treatment, the mortality rate from TB is high. Studies of the natural history of TB disease in the absence of adequate treatment with anti-TB drugs (conducted before drug treatments became available) found that about 70% of individuals with sputum smear-positive pulmonary TB died within 10 years of being diagnosed, as did about 20% of people with culture-positive (but smear-negative) pulmonary TB (W.H.O Global TB report, 2015).

Theoretically, treatment involves the use of combination of antibiotic agents known to exhibit bactericidal and bacteriostatic effects on sensitive *Mycobacterium Tuberculosis* spp. Unfortunately, by some mechanism not completely well understood and some behavioural factors of recipients of these drugs, resistant strains of the organism are proliferating the environment and producing poor clinical outcomes. TB treatment can be challenging for patients as it requires taking multiple drugs for at least 6 months (Sia & Wieland, 2011). A patient is said to have developed drug resistance if the strain causing the disease has become resistant to one or more of the first line anti-TB drugs. Multi-drug resistant TB (MDR-TB) is caused by organisms resistant to at least both isoniazid and rifampicin while extensive drug resistance (XDR-TB) refers to resistant to both Isoniazid and rifampicin plus any fluoroquinolone and a minimum of one of three injectable second line drugs (amikacin, kanamycin or capreomycin). Modelling the emergence of drug resistance is an important research and surveillance strategy that facilitate predicting epidemiological outcome trajectory for the disease. This is very necessary to have a theoretical understanding of the transmission dynamics of both drugs susceptible and drug resistant TB.

Several mechanisms have been proposed to explain the development of resistance to anti-TB medicines. Ecological theory predicts that bacterial fitness plays an important role in the emergence of drug resistance. This theory proposes that drug resistant strain is less fit than the drug susceptible strains. Other recent models which gave room for heterogeneous fitness have over ruled this theory which was rather too simplistic and optimistic in its approach. The classical theory postulates that the emergence of drug resistance is due to selection of pre-existing resistant mutants in the original bacterial population by 'drug pressure'. This is directly related to the duration of regimen being administered to the patients. There are two principal pathways leading to the development of drug-resistant TB: (i) acquired (secondary) drug resistance and (ii) primary drug resistance. These pathways are interconnected and have several culminating factors. Primary resistance occurs in persons who are initially exposed to and infected with resistant organisms. On the other hand, secondary or acquired resistance develops during TB therapy due to inadequate regimen or inappropriate use of anti-TB medicines, wrong prescriptions by healthcare providers, poor quality drugs and the cases of patients stopping treatment prematurely (WHO TB Fact sheets, 2018).

Role of social determinants in treatment

In response to these challenges, the 67th World Health Assembly, in 2014, passed a resolution approving the new post-2015 Global TB Strategy, the END TB strategy, with its ambitious targets and with its vision of ending the TB – as an epidemic disease – by 2030. By 2015, the World Health Organization's End TB Strategy explicitly identified the need to address the social determinants of TB through socio-economic interventions. According to the World Health Organization, "social determinants of health are the conditions in which people are born, grow, live, work and age, including the health system. The distribution of these social and economic conditions among the population influences individual and group differences in health status (WHO, 2011). These determinants influence all stages of TB pathogenesis including risk of exposure, susceptibility to infection, time to diagnosis and treatment and treatment outcome.

There is considerable evidence of the inequality in the distribution of TB prevalence and its mortality in many countries and their

converse relationship with wealth; similarly, there is evidence to show how TB disease has a negative impact on the socio-economic conditions of the patients and their families (Lönnroth *et al.*, 2009).

Gender as a social determinant of treatment outcome

Gender in TB enrolment, treatment and cure rates are not uniform and fully understood. Over 60% of TB incidence occurs in men. In most low and middle-income countries, about two-thirds of reported TB cases are men and only one-third women. It is not clear whether this is due to a higher risk of developing TB among men or under-notification of TB among women. A systematic review and meta-analysis conducted by Horton *et al* also showed that TB prevalence is significantly higher among men than women in low- and middle-income countries, with strong evidence that men are disadvantaged in seeking and/or accessing TB care in many settings (Horton *et al.*, 2016). This may be attributed to differences in social roles, risky behaviours and activities which are more conducive to transmission.

Contrary to this school of thought, *dying for change* reports that men are more likely to access formal health care while women tend to rely on traditional or other alternative health services, because they are cheaper and more socially acceptable. This disparity in access to health care is a reflection of the lack of power of women in society as well as influence of social norms which affects women's mobility. For instance, it is widely accepted that men are entitled to formal healthcare, and the resources needed to secure it before women. Similarly, in Pakistan, women's social status and self -esteem were noted to affect their access to health care (World Bank, 2005).

In some countries, men have been known to have better treatment outcomes than women (Nair *et al.*, 2017), while in other countries it is women who do. It is important to note that 70% of the world's poor are female and that these women face the greatest obstacles to seeking healthcare and getting effective tuberculosis treatment. Epidemiological information also shows that there are differences between men and women in prevalence of infection, rate of progression from infection to disease, incidence of clinical disease, and mortality due to tuberculosis (Holmes *et al.*, 1998). A workshop on gender and tuberculosis concluded that a combination of biological and social factors is responsible for these differences and that knowledge as well as research within this field is insufficient (Diwan *et al.*, 1998).

Also, TB stigma, recognized as a social determinant of health and health inequalities, associated with lack of social support can potentially lead to non-compliance and poor treatment outcome (Sachs, 2012). WHO set the global target rate for a successful treatment outcome for drug resistant TB at 75% and classified treatment outcome as cured, treatment completed, treatment failed, died, loss- to-follow up, not evaluated and treatment success including sum of cured and treatment completed (Jordan & Davies, 2010). Although drug resistant TB can be cured, the cure rate appears to be lower than that of drug susceptible TB. In most studies and systematic reviews, cure rate or treatment completion rates are in a range of 51.6% to 75.3% (Kawatsu *et al.*, 2018; Kibret *et al.*, 2017).

Treatment outcomes are influenced by the social and economic determinants which threaten the gain made so far in TB control. One of the 3 major pillars for the End TB WHO reccommended startegy is the need for social and political action to address the determinants of the disease. To do this effectively, it is important for us to understand the social determinants of health associated with patient's DR-TB drug treatment outcome to inform strategies and interventions to address this promptly.

Behaviour change theories provide the necessary framework for understanding patient's intention to complete treatment and serve as a guide for targeted health interventions. These theories are useful in planning, implementing and evaluating interventions targeted at the behaviour of interest. They help program planners and researchers go beyond basic unchangeable risk factors (e.g. gender, socioeconomic status) to answer why, what and how people can change their behaviour (Glanz and Rimer, 1995). Examples of such theories include the theory of Reasoned Action or Theory of Planned Behaviour (Fishbein and Ajzen, 1975), Health Belief model (Rosenstock, 1974), the model of interpersonal behaviour (Triandis, 1977) and the PRECEDE meta-model

of Green and Kreuter, (2005).These theories focus on multiple levels of the ecological framework from the individual and interpersonal level to the organizational and community levels.

The Theory of Reasoned Action (TRA) and the Theory of Planned Behaviour (TPB) focus on theoretical constructs concerned with individual motivational factors as determinants of the likelihood of performing a specific behaviour. TRA and TPB both assume the best predictor of behaviour is behavioural intention, which in turn is determined by attitude toward the behaviour and social normative perceptions regarding it. TRA proposes that two additional relationships are needed to explain the relationship between attitude and behaviour. First, a favourable attitude toward a behaviour might not be translated into action because of social pressure from significant others not to perform the behaviour.

Empirical review

Several factors including socio-economic and socio-demographic factors have been associated with treatment outcome in drug resistant tuberculosis. Authors in India, Pakistan, Africa, Georgia and Italy have frequently identified baseline and acquired resistance to second line drugs such as Ofloxacin and kanamycin , co-morbid conditions such as HIV, cancer and Diabetes Mellitus , male sex , older age , being overweight , positive sputum smear, non-adherence, previous treatment, longer duration of treatment, treatment in private sectors as factors associated with poor treatment outcome in MDR-TB patients (Kempker *et al.,* 2015;Nair *et al,* 2017; Latif *et al.,*2018; Leveri *et al.,* 2019; Gualano *et al.,* 2019).In three of the studies reviewed, resistance or susceptibility to fluoroquinolone was an independent predictor and risk factor for poor treatment outcome (Alene *et al,* 2017;Parmar *et al*., 2018; Kempker *et al*., 2015). Smoking, alcohol abuse and homeless conditions were other factors found to be significantly associated with unsuccessful treatment outcome (Gualano *et al*., 2019; Leveri *et al*., 2019). Similarly, a systematic review which examined the association between co-morbidities and MDR/XDR-TB revealed that HIV and alcohol misuse were associated with an increased risk of poor treatment outcome in MDR-TB patients (Samuel *et al.,* 2018).

In contrast, the most frequently mentioned factors associated with treatment success with drug resistant tuberculosis have been: use of individually tailored regimen to results of second line drug susceptibility testing in high resource and high burden settings (Olaru *et al;* 2016; Javaid *et al,*2018), adequate funding to ensure availability of second line drug treatment without restrictions, negative sputum culture at 6months (Olaru *et al.,* 2016), provision of psycho-socio economic support (Bhatt *et al.,* 2019; Verdechia *et al.,* 2018) , early detection and management of treatment related adverse event with decrease in proportion of loss-to-follow up (Olaru *et al.,* 2016;Verdechia *et al.,* 2018; Lin *et al.,* 2019; Bhatt *et al.,* 2019).

Previous studies have also shown that women are more likely to adhere to treatment than men which ultimately translates into a higher successful treatment outcome (Hai *et al.,* 2003). In this review, male sex was found to be a predictor of poor treatment outcome which supports findings in existing literature. It has been suggested that males have higher rates of smoking and alcohol consumption, both of which are associated with poor outcomes, and males seem to be less vigilant and less adherent to drug treatment than females (Nair *et al.,* 2017).

Patient's ability to adhere to and complete their treatment regimen plays a key role in treatment success. Other authors have consistently identified male gender, being institutionalized in a place other than prison, positive sputum culture , relapse or retreatment cases , HIV co-infection, having alcoholism, rural residence as factors that increased the likelihood of abandoning TB treatment resulting in poor TB treatment outcome (Maciel *et al.,* 2015; Seid *et al.,* 2018; Evangelista *et al.,* 2018; Adeoti *et al.,* 2018) . In a cross-sectional study conducted in south-west Uganda, successful treatment completion was associated with ongoing counselling support and timely drug refills on the exact appointment date (Mulogo *et al.,* 2017).

Educational interventions

Psychological interventions have been known to improve the prevention and treatment outcome of TB. It is surprising to note that not many studies have focused on educational interventions to reduce non-adherence and its

effect on the treatment outcome in Nigeria. Psychological counselling improved the compliance to treatment and the successful treatment of the disease in an Ethiopian cohort. Tola *et al*. (2016) sought to evaluate the impact of psychological counselling and educational intervention on tuberculosis (TB) treatment adherence in Addis Ababa based on the Health Belief Model (HBM). Findings from this study revealed that at enrolment, the level of non-adherence among intervention (19.4%) and control (19.6%) groups were almost the same.

However, after intervention, non-adherence level decreased among intervention group from 19.4% (at baseline) to 9.5% (at endpoint), while it increased among control group from 19.4% (baseline) to 25.4% (endpoint). The study concluded that Psychological counselling and educational interventions guided by HBM significantly decreased treatment non-adherence level among intervention group. Provision of psychological counselling and health education to TB patients who are on regular treatment is recommended (Tola *et al.,* 2016).

Alipanah *et al.,* (2018) conducted a systematic review involving four randomised control trials and one cohort study. The aim of the study was to evaluate the effect of oral and written educational material as well as counselling on TB treatment outcomes. Findings reported from the study revealed that education and counselling was associated with a higher rate of treatment completion. However, these interventions had no meaningful impact on rates of mortality, treatment success, failure, or loss to follow-up. The authors concluded that TB treatment outcomes are improved with the use of adherence interventions, such as patient education and counselling, incentives and enablers, psychological interventions, reminders and tracers, and digital health technologies (Alipanah *et al.,* 2018).

Baral, Aryal, Bhattrai & Newell (2014) conducted a mixed-method study comprising a formative qualitative study, pilot intervention study and explanatory qualitative study to better understand barriers to the completion of treatment for MDR-TB patients in Nepal. In the resultant pilot intervention study, counselling alone and counselling combined with financial support appeared to improve treatment outcomes: cure rates for those receiving counselling, combined support and no support were 85%, 76% and 67% respectively. The explanatory study demonstrated that both counselling alone and combined counselling and financial support were valued by patients, and that financial and counselling support appear to improve MDR-TB treatment outcomes. The researchers concluded that provision of counselling and financial support may not only reduce their vulnerability, but also increase cure rates (Baral *et al.,* 2014).

Behavioural interventions

A substantial and growing literature in the social sciences demonstrates the potential of behavioural interventions to contribute immensely to public goods. Mobile phones have been instrumental in bringing compliance and thus TB cure for patients. Cross, Rodrigues, D'Souza & Thies, (2014) in their study on 'Using Mobile Phones to Monitor Adherence to Tuberculosis Medications' found that over 90% of all doses were reported correctly using 99DOTS. 99 DOTS is an information communication technology-based treatment adherence mechanism. The system is based on missed call, mobile based Active compliance including Video DOT, and smart pill box. The mechanism has intelligent reminders for patients, alerts for providers and analytics for supervisors. 99DOTS is a cheaper approach for improving the compliance to anti- tuberculosis treatment. There are hidden phone numbers in each anti-TB blister pack which is revealed only after the drug doses are dispensed i.e. when the patient takes the medication. Patient makes a free call to that hidden phone number, thus ensuring the on-time intake of TB medication. As, the sequence of hidden numbers cannot be predicted by the patients but is known only by the system for each blister pack prescribed; the system offers high confidence that patients who respond correctly have indeed taken medication. Liu *et al* (2015) in a study conducted among newly diagnosed active pulmonary TB patients within four provinces in China, used a pragmatic cluster-randomised trial in which 36 districts within four provinces in China were randomly assigned into intervention and control groups using stratification and restriction to one of four case-management approaches.

Patients in the intervention groups received reminders via text messages, a medication monitor, combined, while patients in the control

group received neither (control). Patients in the intervention arms received reminders to take their drugs and reminders for monthly follow-up visits, and the managing doctor was recommended to switch patients with adherence problems to more intensive management or DOT. In all arms (about 1000 per arm), patients took medications out of a medication monitor box, which recorded when the box was opened, but the box gave reminders only in the medication monitor and combined arms. Patients were followed up for 6 months.

In this study, poor adherence was found to be significantly reduced by 42% and 51% in the medication monitor and the combined arms, respectively. Compared to the control arm, the percentage of patient-months with at least 20% of the drug doses missed (called "poor adherence" and measured by pill counts and data from the medication monitor) was not significantly reduced in the text messaging arm. The study concluded that reminders from medication monitors improved medication adherence in TB patients, but text messaging reminders did not and recommends innovative approaches like this to support patients in adhering to TB treatment where universal use of DOT is not feasible (Liu *et al.*, 2015).

Similarly, a systematic review and meta-analysis conducted by Tola *et al* to determine the effect of adherence intervention using different approaches to improve adherence and TB treatment outcome demonstrated an improvement in TB treatment outcome. Medication monitors improved adherence and treatment success with video observed therapy being comparable with DOT. SMS reminders led to a higher treatment completion rate in one RCT and were associated with higher rates of cure and sputum conversion when used in combination with medication monitors. The study concluded that TB treatment outcomes improved when patient education, healthcare provider education, incentives and enablers, psychological interventions, reminders and tracers, or mobile digital technologies were employed (Tola *et al.*, 2016).

Studies have shown that people diagnosed with Tuberculosis tend to discontinue their medication once they start feeling better, especially if they are not on directly observed treatment. About half of all patients with TB, often times, do not complete their treatment and this contributes to prolonged infectiousness, drug resistance, relapse and death (Amuha *et al.*, 2009; Volmink *et al.*, 2000). The reasons for these are not too far- fetched and includes: delay in treatment initiation, access to treatment (Diefenbach-Elstob, Plummer *et al.*, 2017), medication-adherence (Shah *et al.*, 2018), health- seeking behaviour, stigma, gender specific factor, emergence of drug resistance and poor treatment outcomes which reflects in the low treatment success rate observed in the drug resistant TB patient. Consequently, this halts the progress made so far to end TB by the year 2030.

Research problem

Treatment outcomes in MDR-TB are significantly worse than for standard first-line therapy. Worldwide, only 56% of MDR-TB patients are currently successfully treated while about 85% treatment success rate was reported for drug susceptible TB cases (WHO Fact sheet, 2018). According to a report published in *The Lancet Infectious Diseases*, multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) are expected to increase by 2040 in India, the Philippines, Russia, and South Africa, countries that already have a high burden of MDR- TB (Friedrich, 2017). This may sabotage global control efforts to eliminate TB by the year 2030.

Justification for the study

Social determinants of health among several factors have been implicated as responsible for poor treatment outcomes. This includes level of education, marital status and income level (Ali *et al.*, 2017), gender, age, social exclusion, employment and working conditions among others (Patel *et al.*, 2016; Muluye et al 2019).

In Nigeria only a few studies, have examined factors associated with treatment outcomes in the area of TB with majority (Oyefabi *et al.*,2017; Eze *et al.*, 2018; Alobu, Oshi, Oshi & Ukwaja 2014; Sunday, Oladimeji, Ebenezer, Akintunde, Abiola, Saliu *et al.*, 2014;) of these studies focusing on treatment outcomes in drug susceptible TB patients. Moreover, there has been no prior research to assess the impact of social determinants on treatment outcomes in second line DR-TB drug treatment in DR-TB patients accessing home-based DOT strategy in Nigeria.

Societal and scientific relevance

It is hoped that the study will provide us with a holistic and comprehensive approach towards understanding the causal chain of determinants of drug resistant TB and socio determinant factors influencing successful treatment outcome or failure. A better understanding of these risk factors is necessary to design effective interventions that might help reduce morbidity and mortality and thereby improve treatment success. Hence, we hope to promote studies based on theoretical models to develop innovative educational and behavioural interventions in Nigeria in order to improve DRTB treatment success.

Materials and methods

An empirical review of two major categories of studies was conducted globally with regards to adherence, treatment success and failure in tuberculosis and drug resistant tuberculosis. The aim was to assess the overall drug resistant TB treatment success rate and identify potential factors for poor treatment outcomes while looking at interventions to improve adherence and treatment success. Categories reviewed focused on cross-sectional studies that determine factors associated with adherence and treatment outcome in drug resistant TB patients as well as educational and behavioural interventions associated with medication adherence and treatment success.

The review also highlighted problems warranting the study, purpose for the studies, findings and implication of findings to improve on treatment outcomes in drug resistant TB in the future. To the extent possible, it also attempts to identify lessons from experience in high- and low-income settings that might be taken into consideration to guide development of appropriate and effective interventions in resource constrained settings.

Inclusion and exclusion criteria

This analysis included studies from high, middle and low-income countries conducted in different regions of the world and published from 2014 to 2019. The focus was on the determinants of treatment outcome in DR-TB patients; interventions aimed to ensure treatment success; they aimed to measure intention-to-complete treatment as a proxy to adherence. Only studies published in peer review journals were included. Most of the studies relied on 1-5year data (range 1-15 years). Observational studies reported as original research including both qualitative and quantitative studies were included in the review.

The following articles were excluded from this review: studies that focussed on both MDR-TB cases and drug-susceptible TB cases together; studies where full articles were no longer accessed. Articles were excluded if they were not written in English language. Abstracts and case studies were also excluded.

Databases and key strategies

An empirical review of published literature was conducted through a systematic search using Pub Med, Google Scholar and EMBASE databases. The search strategy consisted of a search including medical subject headings (MeSH) terms “treatment outcome” AND “drug resistant tuberculosis” or associated terms for TB and social determinants globally. Relevant indexed studies published between January 2014 and March 2019 were identified (See Figure 1).

Results

Study characteristics

The selection of articles for review was done in three stages: looking at the titles alone, then abstracts and then the full text. From a total of 252 articles obtained through electronic search, 52 were found to be duplicated while 16 were found to be eligible and included in this review *(See Figure 1).*Majority 12 (75%) of the included studies were cross-sectional in nature while 10 (63%) of the studies were retrospective cohort studies, 1 systematic review, 1 was a mixed method study while the remaining 2 were cluster randomized control trials. This review showed that multi drug resistant TB treatment success rate varied from 34.5% to 78.4 %. *(See Table 1).*

Discussion

The treatment success rate seems to be high in about six of these studies ranging from 72.2% to 78.4% with five of the studies reaching the WHO recommended bench mark of 75% treatment success rate in Pakistan, Taiwan, South-Afria, Tanzania and Italy (Javaid *et al*, 2017; Verdecchia *et al.*, 2018; Lin *et al.*, 2019; Gualano *et al*, 2019; Leveri *et al.*, 2019). Among these, the most frequently mentioned factors

associated with treatment success with drug resistant tuberculosis were: use of individually tailored regimen to results of second line drug susceptibility testing in high resource settings, adequate funding to ensure availability of second line drug treatment without restrictions (Olaru *et al.,* 2016; Javaid *et al,* 2017) , trained treatment supporters providing daily DOTS (Javaid *et al,* 2017) status of sputum culture at 6months (Olaru *et al.,* 2016), provision of psycho-socio economic support and patient's enablers (Bhatt *et al.,* 2018, Verdechia *et al.,* 2018) and decrease in proportion of loss-to-follow up (Lin *et al.,* 2019).

Individual-level factors such as being married, educated, HIV-negative, new treatment case and being knowledgeable on TB disease have been shown to increase the odds of successful treatment TB outcomes in Somalia (Ali *et al.,* 2017) .Similarly, provision of psycho-social economic support and early detection and management of treatment-related adverse events have been shown to improve adherence to therapy (Lange *et al.,* 2014).This was supported by a mixed method study conducted in China which demonstrated that DOT and financial support were effective strategies for improving successful treatment outcomes in MDR-TB patients (Yin, Yuan & Hu, 2016; Yin, Wang, Zhou &Wei, 2018). According to these studies, treatment success seems to be high when full directly observed therapy is provided than when patients report on self-administered therapy; directly observed therapy had an indirect positive effect on treatment success mediated through medication adherence. Financial support on the other hand had both a direct and indirect effect on treatment success which was mediated by a self-reported social scale (Yin & Hu 2016; Yin *et al.,* 2018).

Co-morbid conditions like diabetes have been associated with worse treatment outcomes in drug susceptible TB and mentioned as a driver of poor TB treatment outcome in several guidelines or reviews (Maciel & Reis-Santos, 2015). Surprisingly, authors from Pakistan and other countries did not find any significant association between DM and DR-TB treatment outcomes even though death was higher in patients with DM than those without DM (Johnston *et al.,* 2009; Latif *et al.,* 2018; Samuel *et al.,* 2018). This was probably due to the low prevalence of Diabetes Mellitus in the population under study. A common factor with some of the studies reviewed were the long duration of treatment using the conventional treatment regimen consequently leading to more adverse drug reaction, poor adherence, increased LTFU rate and high mortality rate. Many of the factors identified as determinants of poor treatment outcome in this review can be modified using a shorter and easier to follow shorter regimen. DOTS and DOTS plus strategy with continuous psychosocial supports should be emphasized as this improves treatment adherence and overall treatment success rate in highly drug resistant TB in both home-based and facility-based DOT treatment strategy.

Individual management of patients in high resource settings such as Georgia and Italy where there was continuous access to second line and new-anti-TB medications such as bedaquiline and Delamanid also plays key role in achievement of high treatment success rate. This should be accompanied with active drug safety monitoring during the full course of treatment. There is also a need for high level private sector engagement by the national TB program in the control of TB, as the first point of contact of most cases are in private facilities.

Conclusion

The studies reviewed here and most of the studies encountered in literature do not consider the use of conceptual model to determine the factors influencing treatment outcome in drug resistant tuberculosis. They lacked theoretical grounding embedded in a conceptual framework such as the PRECEDE model. They appeared to focus more on the descriptive (Kempker *et al.,* 2015; Nair *et al.,* 2017), clinical (Wang, Pang, Jing, Liu, Wang, Yin *et al.,* 2018) or epidemiological aspects of TB treatment outcome rather than attempt to understand patient's behaviour using behavioural theories.

Consequently, this has deprived us of a holistic and comprehensive approach towards understanding the causal chain of determinants of drug resistant TB and factors influencing successful treatment outcome or failure. Hence, there is a need to promote studies based on theoretical models to develop innovative educational and behavioural interventions in Nigeria in order to improve DR-TB treatment success.

Table 1. Summary of overall treatment outcome of included studies and findings on factors associated with treatment outcome in drug resistant TB patients

Country	Authors	Methods	%Treatment success rate	Favourable outcome factors	Unfavourable outcome factors
Nepal	Baral *et al.*, 2014	Mixed method study		Counselling and financial support	
Georgia	Kempker *et al.*, 2015	Retrospective cohort study	56%		Acquired resistance, sputum smear positivity at 6months
China	Liu *et al*., 2015	Cluster randomised trial		Reminders from medication monitors improved adherence	
Austria	Olaru *et al.*,2016		72.2%	Hospital based	
Ethiopia	Tola *et al.*, 2016	Cluster randomized control trial		Psychological counselling & educational interventions	
China	Alene *et al.*, 2017	Retrospective study	57%		Resistance to Ofloxacin was an independent predictor of poor treatment outcome
India	Nair *et al.*, 2017	Retrospective cohort study	60%		Male sex, age 45 years, being underweight and HIV infection. Adverse drug reactions were reported in 24% of patients, with gastrointestinal disturbance, psychiatric morbidity and ototoxicity the most common.
Pakistan	Javaid *et al.*, 2017	Retrospective cohort study	75.9%	Use of individualized regimen; Trained TS providing daily DOTS Consistent drug supply	Being married, resistance to SLD and presence of XDR-TB
	Alipanah *et al.*,2018	Systematic review		Patient counselling, incentives &	

				enablers, psychological interventions	
India	Bhatt *et al.*, 2018	Retrospective cohort study	Support grp-65% Non-support grp-46%	Psychosocial economic support	
South Africa	Verdechia *et al.*, 2018	Retrospective observational cohort study	75.3%	Low LTFU due to home-based care, Patient enables and Psychosocial support	low BMI and low CD4 count at treatment initiation were associated with an increased risk of unfavourable outcome
India	Parmar *et al.*, 2018	Retrospective cohort study	34.5%		baseline BMI<18; seven missed doses in intensive phase (IP) and continuation phase (CP); cavitary disease; prior treatment episodes characterized by re-treatment regimen taken twice, longer duration and more episodes of treatment; any weight loss during treatment; males and additional resistance to first line drugs (Ethambutol, Streptomycin).
Pakistan	Latif *et al.*, 2018	Cross-sectional study	68.9%		HIV, XDR-TB, exposure to FLD & SLD, previously treated in private sector
Tanzania	Leveri *et al.*, 2019	Retrospective cohort study	75.7%	Presence of chest cavities, Resistance to strep,	Low BMI, smoking, resistance to ethambutol
Italy	Gualano *et al.*,2019	Retrospective cohort study	77%	Tailored regimen, Education on	Smoking, alcohol abuse, homeless condition

				side effect	
Taiwan	Lin *et al.*, 2019	Retrospective data analysis	78.4%	Low proportion of LTFU	

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Reference

[1]. Adeoti, A.O, Oguntiloye, O., Seluwa, A., Orojo, A. (2018). "Drug-Resistant Tuberculosis in South-Western Nigeria: A Case Series" *ARC Journal of Clinical Case Reports;* 4(1): 1-5.

[2]. Ali, M.K., Karanja, S., Karama, M. (2017). *Factors associated with tuberculosis treatment outcomes among tuberculosis patients attending tuberculosis treatment centres in 2016-2017 in Mogadishu, Somalia.Pan Afr Med J,* 2; 28:197. Available at: http://www.worldometers.info/world-population/nigeria-population/(Accessed on 14th May, 2019)

[3]. Alipanah, N., Jarlsberg, L., Miller, C., Linh, N.N., Falzon, D., Jaramillo, E., Payam, N. (2018). Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. PLOS medicine.

[4]. Alobu, I., Oshi, D. C., Oshi, S.N., Ukwaja, K.N. (2014). Profile and determinants of treatment failure among smear-positive pulmonary tuberculosis patients in Ebonyi, South eastern Nigeria. *International Journal of Mycobacteriology*. 3(2):127-131.

[5]. Amuha, M. G., Kutyabami, P., Kittu, F. E., Odoi-Adome, R., & Kalyango, J. N. (2009). Non-adherence to anti-TB drugs among TB/HIV co-infected patients in Mbarara Hospital, Uganda: Prevalence and associated factors. African Health Sciences, 9(S1), 8e15.

[6]. Baker, M., Das, D., Venugopal, K. & Howden-Chapman, P. (2008). Tuberculosis associated with household crowding in a developed country. *J Epidemiol Community Health*, 62(8): 715-21.

[7]. Baral, S.C., Aryal, Y., Bhattrai, King R., Newell, J.N.R. (2014). The importance of providing counselling and financial support to patients receiving treatment for multi-drug resistant TB: mixed method qualitative and pilot intervention studies. *BMC Public Health* 14, 46 (2014). https://doi.org/10.1186/1471-2458-14-46

[8]. Bhatt, R., Chopra, K., Vashisht, R. (2019). Impact of integrated psycho-socio-economic support on treatment outcome in drug resistant tuberculosis-A retrospective cohort study. *India Journal of Tuberculosis* 66: 105-110

[9]. Bloom, B.R., Atun R, Cohen T, Dye, C., Fraser, H., Gomez, G., Salomon, J. Tuberculosis: Holmes, K.K., Bertozzi, S., Bloom, B.R., et al., editors. Major Infectious Diseases. 3rd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017 Nov 3. Chapter 11. Available from: https://www.ncbi.nlm.nih.gov/books/NBK525174/

[10]. Cross, A., Rodrigues, R., D'Souza, G., & Thies, B. (2014) .99DOTS: Using Mobile Phones to Monitor Adherence to Tuberculosis Medications; *Global mHealth Forum. Washington, D.C*

[11]. Diefenbach-Elstob T., Plummer, D., Dowi, R., Wamagi, S., Gula, B., Siwaeya, K., Pelowa, D., Siba, P., Warner, J. (2017). The social determinants of tuberculosis treatment adherence in remote region of Papua New Guinea, *BMC Public Health* 17 (1):

[12]. Diwan V, Thorson A, Winkvist A, eds (1998). Gender and tuberculosis. *NHV report 1998. Göteborg: Nordic School of Public Health, 1998.*

[13]. Duarte A, Lönnrothd K, Carvalh of C, Limaa F, Carvalhog A. C, Mu˜noz-Torricoh M (2017). *Tuberculosis, social determinants and co-morbidities (including HIV).* [Accessed on: 25th March, 2019]

[14]. Evangelista, M.D.N, Maia, R, Toledo, J. P., De Abreu, R.G., Braga, J.U., Barreira, D.and Trajman, A. (2018). Second month sputum smear as a predictor of tuberculosis treatment outcomes in Brazil. *BMC Research Notes.*

[15]. Eze G.U.M, Aduh U. U, Obiebi, I.P., Obodo, K.T.T. (2018). Profile and Treatment Outcomes of Patients with Tuberculosis: A five-year Review of Patients on DOTS in Delta State, Nigeria. *Journal of Community Medicine and Primary Health care,* 30(1):34-46.

[16]. Fishbein and Ajzen, (1975). Belief, Attitude, Intention and Behaviour: An introduction to Theory and Research. Reading, M.A: Addison-Wesley. [Accessed on: 26th March, 2019].

[17]. Gandhi NR, Nunn P, Dheda K, Schaaf HS, Zignol M, Van Soolingen D, Jensen P, Bayona J. (2010). *Multidrug-resistant and extensively drug resistant tuberculosis: a threat to global control of tuberculosis. Lancet. 2010*; 14(9728) :1830-1843.

[18]. Gegia, M., Magee, M.J., Kempker, R.R., Kalandadze, I., Chakhaia, T., Golub, J.E., & Blumberg, H. M. (2015). Tobacco smoking and tuberculosis treatment outcome: A prospective cohort study in Georgia, *Bulletin of the World Health Organ*, 93(6): 390-399. (Accessed on 14th May, 2019).

[19]. Glanz and Rimer, 1995 Glanz, K. and Rimer, B.K. (1995). Theory at a Glance: A Guide for Health Promotion Practice. *National Cancer Institute, Bethesda, MD*. (Accessed on 24th June, 2019).

[20]. GBD Tuberculosis Collaborators (2015). The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. (Accessed on 13th June, 2019).

[21]. Green LW, Kreuter MW. (2005). Health Program Planning: An Educational and Ecological Approach. (4th Edition). New York: McGraw-Hill.

[22]. Gualano, G., Mencarini, P., Musso, M., Mosti, S., Santangelo, L., Murachelli, S., Cannas, A., Di Caro, A., Navarra, A., Goletti, D., Girardi, E., Palmieri, F. (2019). *Putting in harm to cure: Drug related adverse events do not affect outcome of patients receiving treatment for multidrug-resistant Tuberculosis*. Experience from a tertiary hospital in Italy. *PLoS ONE* 14(2).

[23]. Holmes CB, Hausler H, Nunn P. (1998). A review of sex differences in the epidemiology of tuberculosis. International Journal of Tuberculosis and Lung Diseases; 2:96–104.

[24]. Horton, K. C., MacPherson, P., Houben, R. M., White, R. G., & Corbett, E. L. (2016). Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *PLoS medicine*, *13*(9), e1002119. https://doi.org/10.1371/journal.pmed.1002119

[25]. Javaid A, Ullah I, MasudH, Basit A, Ahmad W, Butt Z. A, et al. (2018). Predictors of poor treatment outcome in multidrug-resistant tuberculosis patients: a retrospective cohort study. Clinical Microbiology ans Infection; 24(6), 612-617. https://doi.org/10.1016/j.cmi.2017.09.012.

[26]. Jia Yin, Jinqiu Yuan, Yanhong Hu, Xiaolin Wei (2016). Association between Directly Observed Therapy and Treatment Outcomes in Multidrug-Resistant: A Systematic Review... Jia Yin, Jinqiu Yuan, Yanhong Hu, Xiaolin Wei published 01 Mar 2016.

[27]. Jochem K & Walley J (*1999*). Tuberculosis in high prevalence countries. Current control strategies and theis technical and operational limitations. In: *Tuberculosis: An Interdisciplinary Perspective* (eds Porter JDH & JM Grange). Imperial College Press, London.

[28]. Jordan TS, Davies PD. Clinical tuberculosis and treatment outcomes. The International Journal of Tuberculosis and Lung Disease. 2010;14(6):683–688.

[29]. Johnston, J. C., Shahidi, N. C., Sadatsafavi, M., & Fitzgerald, J. M. (2009). Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PloS one*, *4*(9), e6914. Available at: https://doi.org/10.1371/journal.pone.0006914

[30]. Kawatsu L, Uchimura K, Izumi K, Ohkado A, Yoshiyama T. (2018). Treatment outcome of multidrug-resistant tuberculosis in Japan - the first cross-sectional study of Japan tuberculosis surveillance data. *BMC Infect Dis.* 18(1):445.

[31]. Kempker, R.R., Kipiani, M., Mirtskhulava, V., Tukvadze, N., Magee, M.J., Blumberg, H.M. (2015). Acquired Drug Resistance in *Mycobacterium tuberculosis* and Poor Outcomes among Patients with Multi-drug Resistant Tuberculosis. *Emerging Infectious Diseases* 21(6):992-1001 available at: http://dx.doi.org/10.3201/eid2106.141873 (Accessed on 16th May, 2019).

[32]. Lange, C., Abubakar, I., Alffenaar, J.C., Bothamley, G., Caminero, J.A., Carvalho, A.C.C., ... Cirillo, D. M. (2014). Management of patients with multidrug-resistant/ extensively drug resistant tuberculosis in Europe: a TBNET consensus statement. *Eur Respir J.* 44(1):23-63.

[33]. Latif, A., Ghafoor, A., Wali, A., Fatima, R., Mahboob ul-Haq, Yaqoob, A, Khan, N.M. (2018). Did Diabetes Mellitus affect treatment outcome in drug-resistant tuberculosis patients in Pakistan from 2010 to 2014? *Public Health Action,* 8(1): 14-19.

[34]. Leveri, T.H, Lekule, I, Mollel, E, Lyamuya, F, Kilonzon, K. (2019). Predictors of Treatment Outcomes among Multidrug Resistant Tuberculosis Patients in Tanzania. Volume 2019 |Article ID 3569018 | 10 pages | https://doi.org/10.1155/2019/3569018

[35]. Lin, C. B., Sun, H. C., Chiang, C. Y., Wu, C. W., Chou, H. W., Tang, T. Q., & Lee, J. J. (2019). Treatment outcomes for multidrug-resistant tuberculosis in Eastern Taiwan. *Ci ji yi xue za zhi = Tzu-chi medical journal*, *31*(1): 35–39.

[36]. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. (2015) Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. PLoS Med 12(9): e1001876. doi: 10.1371/journal. pmed.1001876.

[37]. Lonnroth, K., Jaramillo, E., Williams, B.G.,

Dye, C. and Raviglione, M. (2009) Drivers of Tuberculosis Epidemics: The Role of Risk Factors and Social Determinants. Social Science & Medicine, 68, 2240-2246. http://dx.doi.org/10.1016/j.socscimed.2009.03.041

[38]. Maciel, E.L., Reis-Santos, B. (2015). Determinants of tuberculosis in Brazil: from conceptual framework to practical application. *Rev Panam Salud Publica*.;38(1):28–34.

[39]. Millet, J. P., Moreno, A., Fina, L., del Baño, L., Orcau, A., de Olalla, P. G., & Caylà, J. A. (2013). Factors that influence current tuberculosis epidemiology. *European spine journal: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society*, *22 Suppl 4*(Suppl 4), 539–548.

[40]. Mulogo, E. M., Nahabwe, C., Bagenda, F., & Batwala, V. (2017). Determinants of treatment completion among rural smear positive pulmonary tuberculosis patients: a cross-sectional survey conducted in south-western Uganda. *Infectious diseases of poverty*, *6*(1), 104. Available at: https://doi.org/10.1186/s40249-017-0313-3

[41]. Muluye, A.B., Kebamo, S., Teklie, T. & Alemkere, G. *(*2019). Poor Treatment outcomes and its determinants among tuberculosis patients in selected health facilities in East Wollega, Western Ethiopia. *PLoS ONE,* 13(10): e0206227.

[42]. Nair, D., Velayutham, B., Kannan, T., Tripathy, J. P., Harries, A. D., Natrajan, M., & Swaminathan, S. (2017). Predictors of unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India. *Public health action*, *7*(1): 32–38.

[43]. Olaru, I.D., Lange1, C., Indra, A., Meidlinger, L., Huhulescu, S., and Rumetshofer, R. (2016). High Rates of Treatment Success in Pulmonary Multidrug-Resistant Tuberculosis by Individually Tailored Treatment Regimens *Ann Am Thorac Soc*, 13(8):1271-1278. doi: 10.1513

[44]. Oyefabi A, Adetiba E, Leeshak E, Adesigbin O. (2017) Tuberculosis and the determinants of treatment outcome in Zaria, North Western Nigeria – A nine-year (2007–2015) epidemiological review (2017). *J Med Trop*, 19:116-22.

[45]. Parmar, M.M., Sachdeva, K.S., Dewan, P.K., Rade, K., Nair, S.A., Pant, R., Khaparde, S.D. (2018). Unacceptable treatment outcomes and associated factors among India's initial cohorts of multidrug-resistant tuberculosis (MDR-TB) patients under the revised national TB control programme (2007–2011): Evidence leading to policy enhancement. *PLoS ONE* 13(4): e0193903. Available at: https://doi.org/10.1371/journal.pone.0193903

[46]. Patel, S.V., Nimavat, K.V., Alpesh, P.B., Shukla, L.K., Shringarpure, K.S., Mehta, K.G. (2016). Treatment outcomes among cases of multidrug- resistant tuberculosis (MDR-TB) in Wester India: A prospective study. *J Infect Public Health*, 9(4): 478 84.

[47]. Rosenstock, I. M. (1974). Historical Origins of the Health Belief Model. *Health Education Monographs*, *2*(4), 328–335. Available at: https://doi.org/10.1177/109019817400200403

[48]. Sachs, J.D. (2012). From millennium development goals to sustainable development goals. *Lancet*, 379:2206---11.

[49]. Samuels, J.P., Sood, A., Campbell, J.R. *et al.* (2018). Co morbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. *Sci Rep* 8, 4980. Available at: https://doi.org/10.1038/s41598-018-23344-z.

[50]. Seid, M.A., Ayalew, M.B., Muche, E.A., Gebreyohannes, E.A., Abegaz, T.M. (2018). Drug-susceptible tuberculosis treatment success and associated factors in Ethiopia from 2005 to 2017: a systematic review and meta-analysis *BMJOpen.*

[51]. Shah, A.M., Shah, R.B., Dave, N.P. Factors contributing to development of multi-drug resistant tuberculosis (2018). *National Journal of Physiology, Pharmacy and Pharmacology.* 8(10):1463-1469.

[52]. Sia, I.G., Wieland, M.L. (2011). Current concepts in the management of tuberculosis. Elsevier., 6(4):348-361 PubMed/.

[53]. Sulis, G., Roggi, A., Matteelli, A., and Raviglione, M.C. (2014). *Tuberculosis: Epidemiology and Control.* Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4235436/ (Accessed on 16th May, 2019).

[54]. Sunday,O., Oladimeji, O., Ebenezer, F., Akintunde, B., Abiola, T., Saliu, A. (2014), "Treatment Outcome of Tuberculosis Patients Registered at DOTS Centre in Ogbomoso, Southwestern Nigeria: A 4-Year Retrospective Study," Tuberculosis Research and Treatment, vol. 2014, Article ID 201705, 5 pages, 2014. Available at: https://doi.org/10.1155/2014/201705 (Accessed on 16th May, 2019).

[55]. Tola, A., Minshore, K.M., Ayele, Y., Mekuria, A. N. (2019). Tuberculosis Treatment Outcomes and Associated Factors among TB patients Attending Public Hospitals in Harar Town, Eastern Ethiopia: A Five –Year Retrospective Study. *Tuberc Res Treat.* 2019: 1503219. doi: 10.1155/2019/1503219

[56]. Triandis, H.C (1977). Subjective culture and interpersonal relations across cultures. *Annals of the New York Academy of Sciences.* Available at: https://doi.org/10.1111/j.1749-6632.1977.tb29370

[57]. Verdecchia, M., Keus, K., Blankley, S., Vambe, D., Ssonko, C., Piening, T., (2018). Model of care and risk factors for poor outcomes in patients on multi-drug resistant tuberculosis treatment at two facilities in eSwatini (formerly Swaziland), 2011–2013. *PLoS ONE* 13(10): e0205601.

[58]. Wang, Q., Pang, Y., Jing, W., Liu, Y., Wang, N., Yin, H.,.Chu, N. (2018). Clofazimine for treatment of Extensively Drug-Resistant Pulmonary Tuberculosis in China. *Antimicrob. Agents Chemother.*, 62: e02149-17. Available at: https://doi.org/10.1128/AAC02149-17 (Accessed on 16th May, 2019).

[59]. WHO Global TB Report, (2018). Global TB report. Available at: https://www.who.int/tb/publications/global_report/en/ (Accessed on 16th May, 2019)

[60]. WHO TB Fact Sheet. (2018). Available at: https://www.who.int/en/news-room/fact-sheets/detail/tuberculosis

[61]. Yin J, Wang X, Zhou L, Wei X. (2018). The relationship between social support, treatment interruption and treatment outcome in patients with multidrug-resistant tuberculosis in China: a mixed-methods study. *Trop Med Int Health.* 2018; 23(6):668–677.