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

Article by Orekoya, O. Oyepeju¹, Nnodimele O. Atulomah²
¹Public Health, Texila American University, Guyana
²Department of Health Sciences, Cavendish University, Kampala, Uganda
E-mail: pakingbala@yahoo.com¹, annodimele@cavendish.ac.ug²

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 recommened strategy 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 6 months (Olaru et al., 2016), provision of psycho-socio economic support (Bhatt et al., 2019; Verdechia et al., 2018) and 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
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; Alou, 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-Africa, 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 6 months (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 it 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

<table>
<thead>
<tr>
<th>Country</th>
<th>Authors</th>
<th>Methods</th>
<th>% Treatment success rate</th>
<th>Favourable outcome factors</th>
<th>Unfavourable outcome factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal</td>
<td>Baral et al., 2014</td>
<td>Mixed method study</td>
<td></td>
<td>Counselling and financial support</td>
<td>Acquired resistance, sputum smear positivity at 6months</td>
</tr>
<tr>
<td>Georgia</td>
<td>Kempker et al., 2015</td>
<td>Retrospective cohort study</td>
<td>56%</td>
<td>Reminders from medication monitors improved adherence</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>Liu et al., 2015</td>
<td>Cluster randomised trial</td>
<td></td>
<td>Psychological counselling &amp; educational interventions</td>
<td>Resistance to Ofloxacin was an independent predictor of poor treatment outcome</td>
</tr>
<tr>
<td>Austria</td>
<td>Olaru et al., 2016</td>
<td>Cluster randomized control trial</td>
<td>72.2%</td>
<td>Hospital based</td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>Tola et al., 2016</td>
<td>Retrospective cohort study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>Nair et al., 2017</td>
<td>Retrospective cohort study</td>
<td>60%</td>
<td>Male sex, age 45 years, being underweight and HIV infection.</td>
<td></td>
</tr>
<tr>
<td>Pakistan</td>
<td>Javaid et al., 2017</td>
<td>Retrospective cohort study</td>
<td>75.9%</td>
<td>Use of individualized regimen; Trained TS providing daily DOTS Consistent drug supply</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alipanah et al., 2018</td>
<td>Systematic review</td>
<td></td>
<td>Patient counselling, incentives &amp;</td>
<td></td>
</tr>
</tbody>
</table>

Adverse drug reactions were reported in 24% of patients, with gastrointestinal disturbance, psychiatric morbidity and ototoxicity the most common.
<table>
<thead>
<tr>
<th>Country</th>
<th>Authors, Year</th>
<th>Study Design</th>
<th>Support grp (%)</th>
<th>Non-support grp (%)</th>
<th>Psychosocial Economic Support</th>
<th>Psychosocial Economic Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Bhatt et al., 2018</td>
<td>Retrospective cohort study</td>
<td>65%</td>
<td>46%</td>
<td>Psychosocial economic support</td>
<td>low BMI and low CD4 count at treatment initiation were associated with an increased risk of unfavourable outcome</td>
</tr>
<tr>
<td>South Africa</td>
<td>Verdechia et al., 2018</td>
<td>Retrospective observational cohort study</td>
<td>75.3%</td>
<td></td>
<td>Low LTFU due to home-based care, Patient enables and Psychosocial support</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>Parmar et al., 2018</td>
<td>Retrospective cohort study</td>
<td>34.5%</td>
<td></td>
<td></td>
<td>baseline BMI&lt;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).</td>
</tr>
<tr>
<td>Pakistan</td>
<td>Latif et al., 2018</td>
<td>Cross-sectional study</td>
<td>68.9%</td>
<td></td>
<td></td>
<td>HIV, XDR-TB, exposure to FLD &amp; SLD, previously treated in private sector</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Leveri et al., 2019</td>
<td>Retrospective cohort study</td>
<td>75.7%</td>
<td></td>
<td>Presence of chest cavities, Resistance to strep.</td>
<td>Low BMI, smoking, resistance to ethambutol</td>
</tr>
<tr>
<td>Italy</td>
<td>Gualano et al., 2019</td>
<td>Retrospective cohort study</td>
<td>77%</td>
<td></td>
<td>Tailored regimen, Education on smoking</td>
<td>Smoking, alcohol abuse, homeless condition</td>
</tr>
</tbody>
</table>
Taiwan | Lin et al., 2019 | Retrospective data analysis | 78.4% | Low proportion of LTFU

Acknowledgements

The authors express appreciation to all the research assistants who facilitated desk review through database search and documentations.

Reference


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


