Tuberculosis treatment outcomes in patients with resistant tuberculosis at a district hospital in Kwazulu-Natal Province of South Africa

***Ntambwe Malangu*[1] *and Modinat O. Ibrahim*[2]**

Abstract

This study purported to investigate factors associated with treatment outcomes among MDR-TB and XDR-TB patients treated at Greytown hospital. This was a cross-sectional study based on a review of medical records of patients that have been treated at Greytown hospital for drug resistant tuberculosis from January 2011 to December 2012. A data collection form designed for the study was used. The data that was collated included socio-demographic variables, clinical data including details of treatment given and adverse effects as well as outcomes of treatment. Descriptive and inferential statistics were calculated. Overall, 127 records were found that met the inclusion criteria for this study during the study period. The mean age of patients was 36.9±11.9 years, ranging from 12 to 82 years. Based on the median age of 34 years, 54.3% were over 34 years old. The majority of patients were females (56.7%), unemployed (89.8%) and the marital status of (78.7%) patients was not recorded in the files. Overall, 55.1% were females aged 34 years and older. The majority of patients suffered from pulmonary tuberculosis; only 3 cases (2.4%) were extra-pulmonary, while 72 (56.7%) suffered from multi-drug resistant tuberculosis (MDR-TB), and 55 (43.3%) had extended drug-resistant tuberculosis (XDR-TB). They took their treatment fairly well as about 70% of them adhered to treatment. Overall, the outcomes of treatment success was poor as only 29.9% had completed the treatment and confirmed cured, while 18.1% had died. In addition to being unemployed, clinical factors associated with being cured were namely, taking the treatment for the correct duration and adhering to treatment. On the contrary, failing to take the treatment correctly was associated with death. In conclusion, the treatment success among patients with resistant tuberculosis was 29.9%. Adherence to treatment for the correct duration of treatment was significantly associated with the success of treatment.

Key words*:* tuberculosis, resistant, treatment outcomes, risk factors

[1] School of Public Health, Sefako Magkatho Health Sciences University, email: gustavmalangu@gmail.com
[2] School of Public Health, Sefako Magkatho Health Sciences University, email: horlydey2004@yahoo.com

Background

Resistant tuberculosis (TB) is a worldwide problem. It is known that over 90 countries have reported cases of multi-drug resistant tuberculosis (MDR-TB). In Sub-Saharan Africa, it is now considered as a serious challenge due to the fact that it is strongly associated with HIV/AIDS pandemic (Zignol et al, 2006; Bantubani et al, 2014). An estimated 1.1 million (13%) of the 8.6 million people who developed TB in 2012 were HIV-positive. In 2012, an estimated 450 000 people developed MDR-TB and there were 170 000 deaths from MDR-TB (WHO, 2013). South Africa ranks as the third highest country in the world in terms of TB incidence and the one with the highest number of MDR-TB and extended drug-resistant tuberculosis (XDR-TB) in the African region (Bantubani et al, 2014; WHO, 2013). Though several cases of resistant-TB have been reported throughout South Africa, the highest prevalence of MDR-TB and XDR-TB has been recorded in Kwazulu Natal province, especially Umzinyathi and Umkhanyakude districts (Gandhi et al., 2006; Wallengreen et al, 2011). This explains why a specialized unit for treating MDR-TB was established at Greytown hospital.

Some studies have reported that MDR- TB patients were not effectively treated and this has contributed to the rise in the number of XDR-TB (Holtz et al, 2006; Mlambo et al, 2008). Between 2009 and 2010, the number of cases of XDR-TB diagnosed in South Africa by the National Health Laboratory Services increased from 594 to 741; while the treatment success rate has been reported to be below 50%, with a default rate of 30% (Shean et al, 2008; Shah et al, 2011; NDoH, 2011). These negative statistics necessitate the evaluation of possible related factors. The association between the treatment outcomes and factors relating to the patients circumstances and clinical status needs to be assessed in order to identify areas to be targeted with interventions in order to improve the outcomes of treatment in patients with MDR and XDR-TB. Hence, this study purported to investigate factors associated with treatment outcomes among MDR-TB and XDR-TB patients treated at Greytown hospital. It is hoped that the findings from the study could be used by clinicians, decision-makers, and institutional managers to design and implement relevant interventions.

Methods

Study design and setting

This cross-sectional study based on a review of patients' medical records was conducted at Greytown Hospital. This is a district hospital located in the south of the Kwazulu-Natal province of South Africa. This province is one of the most affected by the double epidemic of tuberculosis and HIV. The study was conducted by reviewing the records of patients treated at this facility from first November 2013 to the end of January 2014. Data were collected using a data collection form designed for the study. The data collated included socio-demographic variables, clinical data including details of treatment given, adverse effects, as well as outcomes of treatment.

Population

The study population comprised of medical records of TB patients registered as MDR and XDR cases in the TB register at Greytown Hospital. Records of all patients that were treated at the health care facility during the study period, from January 2011 to December 2012, were included in this study irrespective of age and sex.

Ethical considerations

Ethics approval for the study was obtained from the Medunsa Research Ethics Committee. Permission to conduct, retrieve, and access patients' records was obtained from institutional managers.

Data analysis

Data were double captured into a Microsoft Excel spreadsheet and imported into STATA 10 for data analysis. Descriptive and inferential statistics were calculated. For the comparison of categorical variables, cross-tabulation was performed in order to assess the association between variables; the Pearson's chi-square test was calculated to determine the statistical significance of relationships between variables. The level of statistical significance was set at <0.05 (Somekh and Lewin, 2005).

Results

Sociodemographic profile of patients

The mean age of patients was 36.9±11.9 years, ranging from 12 to 82 years. Based on the median age of 34 years, 54.3% (69 cases) were over 34 years old. The majority of patients were females (56.7%), unemployed (89.8%), and the marital status of (78.7%) patients was not recorded in the files. Overall, 55.1% were females and aged 34 years and older (Table 1).

Table 1: Socio-demographic characteristics of patients

Variables	Frequency	Percent
Sex		
Male	55	43.3
Female	72	56.7
Age category		
<34 years	58	45.7
34 years and older	69	54.3
Employment status		
Unemployed	114	89.8
Employed	13	10.2
Marital status		
Single	17	13.4

Married	7	5.5
Divorced	3	2.4
Unknown	100	78.7

Clinical profile of patients

The majority of patients suffered from pulmonary tuberculosis; only 3 cases (2.4%) were extra-pulmonary; two of the three cases affected lymph nodes, and one case affected the spine. Based on the reports on drug sensitivity testing, 72 (56.7%) patients in the sample had MDR tuberculosis; while 55 (43.3%) had XDR tuberculosis. Although not statistically significant, XDR-TB affected more females than males (62.3% versus 37.7%, p=0.13); more patients aged 34 years old and older than the younger ones (56.4% versus 43.6%, p=0.69); slightly more of those unemployed than those with employment (90.9% versus 9.1%, p=0.81).

The majority of patients (91.7%) were co-infected with HIV; few patients suffered also from diabetes (3.7%), hypertension (3.7%) and alcohol abuse (0.9%) as co-morbidities. In addition, some of these patients were obese. The percentage of patients who were obese increased from 11.8% at the start of the treatment to 18.9% some months later after the treatment.

Table 2 presents types of documented common adverse drugs reactions. The results indicate that adverse effects of drugs prescribed were documented in 61(48.4%) patients; among them, 32 (52.5%) patients had MDR-TB; the remaining suffered from XDR-TB. The most common ADR documented were vomiting, anemia and peripheral neuropathy. Of the ADRs documented, the majority (71.7%) was graded as not serious or mild; 13.3% were of moderate severity; while 15% were severe.

Table 2: Adverse drug reactions documented

Adverse effects	**Frequency**	**Percent**
Vomiting	17	27.9
Anaemia	15	24.6
Peripheral Neuropathy	15	24.6
Skin rashes	4	6.6
Ototoxicity	3	4.9
Psychiatric conditions	3	4.9
Nausea	1	1.6
Headache	1	1.6
Gynecomastia	1	1.6
Heartburn	1	1.6

There was no statistically significant difference with regard to severity based on the types of TB; ADR of moderate severity were documented almost equally in both groups (12.5% in MDR-TB versus 14.3% in XDR-TB, p=0.75). Of the 9 severe ADRs, 7 (5.5%) led to hospitalisation, 2 (1.6%) to some disability and 2 (1.6%) to treatment interruption in patients affected. Other reasons for treatment interruption were loss to follow-up (4 cases), poor adherence (3 cases), planned interruption (1 case), treatment failure (1 case), and death (1 case).

The initial regimen for tuberculosis treatment was prescribed to 97.7% (124 cases) of patients. The MDR-TB regimen was made of kanamycin, ethionamide, ofloxacin, pyrazinamide, cycloserine or ethambutol. The standard regimen containing ethambutol was used in 69 cases (54.3%). Up to the time of data collection, some 53.5% of MDR-TB patients had received treatment for 6 months, 32.3% for 18 months. Before being transferred, XDR-TB patients were prescribed a regimen made of moxifloxacin, terizidone, pyrazinamide, ethionamide, and para-aminosalicylic acid (PAS). About 69.3% and 72.2% of patients achieved at least an 80% adherence with regard to the initial and MDR regimens respectively. Overall, in 12 patients' records (9.4%), it was recorded that these patients had been taking unspecified traditional medicines.

Outcomes of treatment

Overall, the treatment success was 29.9% as 28.3% and 1.6% of patients respectively were confirmed cured and had completed the treatment. However, the cure status was not known of about half of the patients because they were either transferred out (33.1%) or undetermined (15.7%) as they were still on treatment. Of those who defaulted, only 3 cases were traced (3.2%), and one case was confirmed as a failed treatment (Table 3).

The reason for transferring patients was that they had XDR-TB, therefore, they needed to be attended by a specialist facility. A case fatality of 18.1% was reported; the two recorded causes of death were tuberculosis in 17 cases (13.4%) and co-morbid conditions in 6 cases (4.7%).

Table 3: Outcomes of treatment

Outcomes of treatment	Frequency	Percent
Cured	36	28.3
Completed	2	1.6
Defaulted	3	2.4
Failed	1	0.8
Transferred out	42	33.1
Died	23	18.1
Undetermined	20	15.7

With regard to factors associated with being cured, most of the clinical factors that were assesses were actually associated (Table 4). The factors significantly associated with being cured were not having interrupted treatment; taking the initial regimen for 6 months and the MDR regimen for 18 months, as well as achieving at least 80% adherence to both regimens. It is interesting to note that MDR-TB patients were more likely to be cured than those who suffered from XDR-TB. The only sociodemographic variable assessed that was significantly associated with being cured was being unemployed. Patients who were unemployed were about five times more likely to be cured than those who were employed (p=0.01).

Table 4: Factors associated with being cured

Factors	OR (95% CI)	p-value
Over 34 years old versus younger	1.19 (0.55, 2.62)	0.66
Females versus males	1.09 (0.49, 2.43)	0.83
Not married versus others	1.93 (0.68, 6.23)	0.22
Unemployed versus employed	4.75 (1.45, 15.88)	**0.01**
MDR patients versus XDR patients	49.62 (7.44, 2052.81)	**0.0001**
Taking the initial treatment for 6 months versus not	5.2 (1.93, 15.39)	**0.0003**
Taking the MDR-TB treatment regimen for 18 months versus not	68.00 (7.32, 2954.47)	**0.00001**
Achieving at least 80% adherence to initial treatment versus not	4.76 (1.48, 19.91)	**0.005**
Achieving at least 80% adherence to MDR-TB treatment regimen versus not	27.00 (3.30, 1184.96)	**0.0001**
Did not used Traditional medicines versus used	2.10 (0.41, 20.59)	0.51
Did not interrupted versus those who interrupted	248.2 (30.84, 1994.00)	**0.00001**
ADR documented versus not	1.03 (0.43, 2.41)	0.99
Suffered ADRs of mild severity versus those who suffered from severe ADRs	4.17 (0.84, 20.73)	**0.07**

Moreover, with regard to factors associated with dying, numerically the majority of patients who died were younger than 34 years old and unemployed who suffered from MDR-TB. However, upon assessment of factors significantly associated with dying, the factors so associated were having suffered from severe ADRs, failing to take the initial regimen for 6 months and the MDR-TB regimen for 18 months as well as failing to achieve at least 80% adherence to both regimens. Interestingly, having suffered from ADRs or having taken traditional medicines did not show any association with dying in this study. Similarly, all sociodemographic variables assessed were not significantly associated with dying. However, it was found that 21 out 23 patients (91.3%) who died were also co-infected with HIV (Table 5).

Table 5: Factors associated with death among patients

Factors	OR (95%CI)	p-value
Patients younger than 34 years old versus older	2.17 (0.86, 5.47)	0.10
Males versus females	1.28(0.46, 3.49)	0.65
Married versus unmarried	2.69 (0.98, 7.38)	0.07
Employed versus unemployed	2.90 (0.36, 23.51)	0.33
Those who interrupted versus those who did not	2.5 (0.49, 10.45)	0.16
Those who suffered severe ADRs versus those with mild ADRs	4.15 (1.06, 16.21)	**0.034**
Did not take initial treatment for 6 months versus those who did	5.53 (1.77, 20.30)	**0.0010**
Did not take MDR treatment for 18 months versus those who did	160.00 (13.00, 688.68)	**0.00001**
Did not achieve 80% adherence to initial treatment versus who did	3.90 (1.4, 11.13)	**0.0053**
Did not achieve 80% adherence to MDR treatment versus who did	144 (13.08, 6267.99)	**0.00001**
Used traditional medicines versus who did not	0.89(0.09, 4.68)	0.99

Discussion

The findings from this study showed that the majority of patients who suffered from resistant tuberculosis at Greytown hospital were females and over 34 years old. The background of these patients could be described as disadvantageous as many of them were unemployed. This profile is similar to reports by Porwal and co-workers (2013) who found that more than a third of MDR-TB and XDR-TB patients were also female and from disadvantaged communities. Clinically, these patients suffered from some co-morbid conditions, of which, the most common was HIV. This finding concurs with several reports that have indicated that the HIV pandemic has exacerbated the incidence of tuberculosis (Shean et al, 2008; Otwombe et al, 2013). As reported in other settings, this study found also that the majority of patients were affected by adverse drug reactions of mild severity. Although the adherence rate was relatively high in comparison to reports from other settings, the outcomes of treatment were poor (Shean et al, 2013; Brust et al, 2013; O'Donnell et al, 2013).

The overall cure rate was 28.3% while the case fatality rate was 18.1%. In these respects, the findings from this study concur with reports by other investigators who reported poor cure rates and high mortality in patients with resistant tuberculosis (Satti et al, 2012; O'Donnell et al, 2013). The success of treatment from this study setting is far less better as compared to what has been reported in Gauteng Province where it was about 49% (Marais et

al, 2014). Given the overall low cure rate, it seems that preventing the onset of MDR-TB and XDR-TB is a more effective strategy; hence, it is necessary that the national and provincial health care facilities should adopt new technologies for identifying resistance early. Moreover, drug regulatory authorities should ensure a mechanism for a quick phasing-in of new drugs that can help curtail the onset of drug resistance (Zumla et al, 2013).

Among the factors associated with treatment outcomes, it is interesting to note that being unemployed appeared to be associated with being cured. This finding suggests that unemployed people adhered more to their treatment may be because they could stay in the hospital and be cared for than those in employment who may have left the hospital to go back to their workplaces. In addition to being unemployed, clinical factors were associated with being cured were namely, taking the treatment for the correct duration and adhering to treatment. On the contrary, failing to take the treatment correctly was associated with death. The findings of this study contrast with reports from Western Cape Province of South Africa, where it was reported that loss to follow-up and age, particularly older age was associated poor treatment outcomes (Moyo et al, 2015).

Hence, healthcare providers and policy-makers should create an enabling environment so that patients who are in full employment can adhere to treatment. Hence, people that are employed who have been diagnosed with resistant tuberculosis should be given extended medical leave beyond the current 6 months applicable to all workers. This is because the findings from this study have shown that taking the initial regimen for 6 months and the MDR regimen for 18 months was associated with being cured. Moreover, the findings that most patients transferred had been having XDR-TB suggest the need for the establishment of more specialised facilities within the province of KwaZulu-Natal. This finding underscores the influence of health care system in outcomes of treatment (Loveday et al, 2014).

With regards to mortality, the influence of co-morbidities, namely, HIV could be noted as more than 90% of patients who died were co-infected with this condition. It is possible also that HIV could be one of the factors that led to resistance in the first instance. This phenomenon has been explained considering the possibility that HIV may lead to malabsorption of TB drugs and acquired rifampicin resistance (Wells et al, 2007). The finding from this study concurs with reports by Satti and co-workers (2012) who reported that 70% of patients with MDR-TB were HIV-positive. Schnippel and co-investigators (2015) have reported from a large cohort study that, indeed, people with HIV, whether on treatment or not are at least more likely to die from resistant tuberculosis than those who are HIV-negative. Other co-morbidities were diabetes and obesity among others. Diabetes has been reported as a common co-morbidity associated with drug-resistant TB by other investigators (Hsu et al, 2013; Magee et al, 2013). In other settings, the presence of co-morbidities has been documented to be associated with negative outcomes. Baker and co-

workers (2011) pointed out that diabetes is associated with an increased risk of treatment failure and death during tuberculosis treatment.

With regard to adverse drug reactions (ADRs), this study has shown that although they were common; their impact was limited; none of them resulted in death but less than 10% led to hospitalisation and treatment interruption. These findings contrast with reports from other settings where ADRs have been associated with negative outcomes (Shin et al, 2007; Bezu et al, 2014; Scheelbeek et al, 2014; Huang et al, 2015). However, the distribution of ADRs in this study was similar to what has been reported by other investigators who noted that nausea, vomiting, diarrhea and other GIT symptoms were the most common ADRs (Shean et al, 2008; Shean et al, 2013; Zala et al, 2015).

As limitations, this study was based on the review of records; hence inherent design limitations such as the incompleteness of data were noted. For instance, data on marital status could not be found in several records. Secondly, as a cross-sectional study, causal links could not be established due to the lack of temporal connection.

Conclusions

In conclusion, resistant tuberculosis affected mainly people of disadvantageous backgrounds who were unemployed. The treatment success among patients with resistant tuberculosis was 29.9%. The outcomes of treatment were poor with low cure rate and a relatively high mortality. Adherence to treatment for the correct duration of treatment was significantly associated with the success of treatment.

Authors' contributions

NM and MIO conceptualized the study, MIO collected data; NM performed the analysis; NP drafted the paper. All authors contributed intellectual inputs and approved the paper.

Acknowledgements

The institutional managers at the study site are hereby acknowledged for the immense support during data collection.

References

Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, ... & Murray MB. (2011). The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Medicine*, *9*(1), 81.

Bezu, H., Seifu, D., Yimer, G., & Mebrhatu, T. (2014). Prevalence and Risk Factors of Adverse Drug Reactions Associated Multidrug Resistant Tuberculosis Treatments in Selected Treatment Centers in Addis Ababa Ethiopia. *Journal of Tuberculosis Research*, 2, 144-154

Bantubani, N., Kabera, G., Connolly, C., Rustomjee, R., Reddy, T., Cohen, T., & Pym, A. S. (2014). High rates of potentially infectious tuberculosis and multidrug-resistant tuberculosis (MDR-TB) among hospital inpatients in KwaZulu Natal, South Africa indicate risk of nosocomial transmission. PloS one, 9(3), e90868.

Brust JC, Shah NS, van der Merwe TL, Bamber S, Ning Y, Heo M, ... & Gandhi NR. (2013). Adverse events in an integrated, home-based treatment program for MDR-TB and HIV in KwaZulu-Natal, South Africa. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *62*(4), 436.

Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, ... & Friedland G. (2006). Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *The Lancet*, *368*(9547), 1575-1580.

Hsu AH, Lee JJ, Chiang CY, Li YH, Chen LK, & Lin CB. (2013). Diabetes is associated with drug-resistant tuberculosis in Eastern Taiwan [Short communication]. *The International Journal of Tuberculosis and Lung Disease*, *17*(3), 354-356.

Huang, F. L., Jin, J. L., Chen, S., Zhou, Z., Diao, N., Huang, H. Q., ... & Zhang, W. H. (2015). MTBDRplus results correlate with treatment outcome in previously treated tuberculosis patients. *The International Journal of Tuberculosis and Lung Disease*, *19*(3), 319-325.

Holtz TH, Sternberg M, Kammerer S, Laserson KF, Riekstina V, Zarovska E, ... & Leimane V. (2006). Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. *Annals of Internal Medicine*, *144*(9), 650-659.

Loveday, M., Padayatchi, N., Wallengren, K., Roberts, J., Brust, J. C., Ngozo, J., ... & Voce, A. (2014). Association between health systems performance and treatment outcomes in patients co-infected with MDR-TB and HIV in KwaZulu-Natal, South Africa: implications for TB programmes. *PloS one*, *9*(4), e94016.

Magee MJ, Bloss E, Shin SS, Contreras C, Huaman HA, Ticona JC., ... & Cegielski JP. (2013). Clinical characteristics, drug resistance, and treatment outcomes among tuberculosis patients with diabetes in Peru. *International Journal of Infectious Diseases*, *17*(6), e404-e412.

Marais, E., Mlambo, C. K., Lewis, J. J., Rastogi, N., Zozio, T., Grobusch, M. P., ... & Warren, R. W. (2014). Treatment outcomes of multidrug-resistant tuberculosis patients in Gauteng, South Africa. *Infection*, *42*(2), 405-413.

Mlambo CK, Warren RM, Poswa X, Victor TC, Duse AG, & Marais E (2008). Genotypic diversity of extensively drug-resistant tuberculosis (XDR-TB) in South Africa. *The international journal of tuberculosis and lung disease*, *12*(1), 99-104.

Moyo, S., Cox, H. S., Hughes, J., Daniels, J., Synman, L., De Azevedo, V., ... & van Cutsem, G. (2015). Loss from treatment for drug resistant tuberculosis: risk factors and patient outcomes in a community-based program in Khayelitsha, South Africa. *PloS one*, *10*(3).

National Department of Health (NDOH). Management of drug-resistant Tuberculosis. MDR-TB: Policy guidelines. 2011.

O'Donnell MR, Padayatchi N, Kvasnovsky C, Werner L, Master I, & Horsburgh Jr CR. (2013). Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. *Emerging Infectious Diseases*, *19*(3), 416.

Otwombe KN, Variava E, Holmes CB, Chaisson RE, & Martinson N. (2013). Predictors of delay in the diagnosis and treatment of suspected tuberculosis in HIV co-infected patients in South Africa. *The International Journal of Tuberculosis and Lung Disease*, *17*(9), 1199-1205.

Porwal C, Kaushik A, Makkar N, Banavaliker JN, Hanif M, Singla R, ... & Singh UB. (2013). Incidence and risk factors for extensively drug-resistant tuberculosis in Delhi region. *PloS one*, *8(2).*

Satti H, McLaughlin MM, Hedt-Gauthier B, Atwood SS, Omotayo DB, Ntlamelle L, & Seung KJ. (2012). Outcomes of multidrug-resistant tuberculosis treatment with early initiation of antiretroviral therapy for HIV co-infected patients in Lesotho. *Journal of Acquired Immune Deficiency Syndromes (1999)*, 62(4), 436.

Shah NS, Richardson J, Moodley P, Moodley S, Babaria P, Ramtahal M, ... & Gandhi NR. (2011). Increasing drug resistance in extensively drug-resistant tuberculosis, South Africa. *Emerging Infectious Diseases*, *17*(3), 510.

Shean K, Streicher E, Pieterson E, Symons G, van Zyl Smit R, Theron G, ... & Dheda K (2013). Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa. *PLOS one 2013*, 8(5) e 63057.

Shean KP, Willcox PA, Siwendu SN, Laserson KF, Gross L, Kammerer S, ... & Holtz TH. (2008). Treatment outcome and follow-up of multidrug-resistant tuberculosis patients, West Coast/Winelands, South Africa, 1992–2002. *The International Journal of Tuberculosis and Lung Disease*, *12*(10), 1182-1189.

Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, Keshavjee S et al. (2007). Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. *The International Journal of Tuberculosis and Lung Disease*, *11*(12), 1314-1320.

Scheelbeek, P. F., Wirix, A. J., Hatta, M., Usman, R., & Bakker, M. I. (2014). Risk factors for poor tuberculosis treatment outcomes in Makassar, Indonesia. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *45*(4), 853-858.

Schnippel, K., Shearer, K., Evans, D., Berhanu, R., & Ndjeka, N. (2015). Predictors of mortality and treatment success during treatment for rifampicin-resistant tuberculosis within the South African National TB Programme, 2009 to 2011: a cohort analysis of the national case register. *International Journal of Infectious Diseases*.

Somekh B, & Lewin C. (2005). *Research methods in the social sciences*. Sage.

Wallengren K, Scano F, Nunn P, Margot B, Buthelezi SS, Williams B, ... & Pillay Y. (2011). Drug-resistant tuberculosis, KwaZulu-Natal, South Africa, 2001–2007. *Emerging Infectious Diseases*, *17*(10), 1913.

Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, ... & Weyer K. (2007). HIV infection and multidrug-resistant tuberculosis—the perfect storm. *Journal of Infectious Diseases*, *196*(Supplement 1), S86-S107.

World Health Organization 2013. Global tuberculosis report. World health organization. Geneva.

Zala, A. C., Manvar, R., Patel, D., Patel, D., & Gamit, N. (2015). A Prospective-Observational Study to Assess the Prevalence of Adverse Drug Reactions in MDR-TB Patients at Tertiary Care Hospital in India. *American Journal of Pharmacology and Pharmacotherapeutics*, *2*(4), 112-119.

Zignol M, Hosseini MS, Wright A, Lambregts–van Weezenbeek C, Nunn P, Watt CJ, ... & Dye C. (2006). Global incidence of multidrug-resistant tuberculosis. *Journal of Infectious Diseases*, *194*(4), 479-485.

Zumla A, Nahid P, & Cole ST. (2013). Advances in the development of new tuberculosis drugs and treatment regimens. *Nature Reviews Drug discovery*, *12*(5), 388-404.