OPTIMIZING TUBERCULOSIS TREATMENT SUCCESS RATES IN NAMIBIA

A RESEARCH THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY IN CLINICAL PHARMACOLOGY

OF

THE UNIVERSITY OF NAMIBIA

BY

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September 2019

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ABSTRACT

Tuberculosis (TB) is a leading cause of mortality globally, leading to an annual death rate of 1.8 million. In 2017, over 700 people died from TB in Namibia. Moreover, despite the scale-up of high-quality Directly Observed Treatment Short Course strategy (DOTS) to control TB in Namibia, treatment success rates (TSR) fall short of the global target of 90%. Unsuccessful treatment outcomes are a risk drug resistant TB. Consequently, the study aimed to model the population, patient and drug (pharmacokinetics and pharmacovigilance) level predictors of treatment success, cure and completion rates under the DOTS programme in Namibia.

The study was designed in four phases, population, and patient and drug level models, and an overall conceptual model to optimize TSR. Population-level modeling of the effectiveness of the community based-DOTS on TSR, cure and completion was done using interrupted time-series analysis. Three patient level models of TSR, loss to-folow-up (LTFU) and case fatality rates for a 10-year nationwide cohort, 2004-2016 were conducted using multivariate regression in R. Two drug level studies, i.e. a meta-analysis of the impact of HIV/TB co-infection on serum concentrations (Cmax) of rifampicin, isoniazid, pyrazinamide and ethambutol, as well as a systematic review on the burden of adverse effects were modeled.

First, the CB-DOTS intervention in 2005, immediately increased annual TSR by 12.9% ($p < 0.001$) and then by 1.1%/year thereafter, but stagnated at ~85% by 2015. Secondly, the independent predictors for TSR were region of DOTS implementation ($p=0.001$); type of Workbased DOT supporter ($p<0.001$), sputum conversion at 2 months ($p=0.013$); cotrimoxazole prophylaxis OR= 0.4(95%CI: 0.2, 0.7, $p=0.002$); HIV co-infection OR=0.2(95%CI: 0.1, 0.5, $p=0.001$) and the DOT regimen ($p<0.001$). Thirdly, the annual decline in cases LTFU was significant between the first (2005-2010) and second (2010-2015) medium term plan periods for TB programme implementation ($p=0.002$).The independent predictors of LTFU were male sex ($p=0.004$), 15-24 age group ($p=0.03$), provider of treatment ($p<0.001$), intensive phase ($p=0.047$) and living in border/transit regions ($p<0.001$). Fourthly, the independent predictors of TB case-fatality under the DOTS programme were HIV coinfection OR=0.2 (95%CI: 0.1, 0.4, $p=0.001$) and the non-

assessment of drug resistant testing using a GeneXpert, OR=3.4 (95%CI: 1.6, 7.5, p=0.003), region of DOTS implementation (p<0.001), patients age (p<0.001) and cotrimoxazole prophylaxis (p=0.013). Fifthly, the meta-analysis showed that HIV/AIDS significantly lowered C_{max} of rifampicin -1.11µg/mL (95%CI: -2.18, -0.04, p=0.04, I^2=0%) and ethambutol -0.75 µg/mL (95%CI: -1.38, -0.13, p=0.02, I^2=0%) in the African population. Lastly, upto 69% of hospitalized patients experienced at least one adverse events, mainly of Type-A (i.e. predictable adverse drug reactions, range 9% to 69%). The frequency of adverse reactions was higher among TB patients with; HIV co-infection (78.5%, p=0.003), low baseline body weight (p=0.002), ART (76.2%, p=0.012) or cotrimoxazole prophylaxis (78%, p=0.005).

A conceptual model for optimizing TSR was developed. We conclude, current DOTS programme though effective, is inadequate to optimize TSR and end TB by 2035. HIV/TB co-infection is main predictor of poor TSR at population, patient and drug level. Programmatic (i.e. access to bacteriological and drug resistance testing, quality of DOTS services by region), clinical (HIV/TB coinfection) and social-economic (quality of DOT supporter and young/middle aged males). The comprehensive integration of TB/HIV services as well as targeted programmatic, clinical and treatment interventions are required to enhance DOTS treatment success in Namibia. Further efforts are needed to individualize dosage regimens with rifampicin and ethambutol, and monitor C_{max} in HIV co-infected patients in Africa to improve treatment outcomes.

KEY WORDS: Namibia; Optimize; Treatment Success, Tuberculosis

LIST OF PUBLICATION(S)/CONFERENCE(S) PROCEEDINGS

Related to this thesis (publications)

1. **Kibuule, D.,** Rennie, T. W., Nunurai, R., Mavhunga, F., Thomas, A., Amutenya, R., & Verbeeck, R. K. (2019). Effectiveness of the community-based DOTS strategy on tuberculosis treatment success rates in Namibia. *The International Journal of Tuberculosis and Lung Disease*. 2019 Apr 1;23(4):441-9
2. **Kibuule D**, Verbeeck RK, Nunurai R, Mavhunga F, Ene E, Godman B, Rennie TW. (2018). Predictors of tuberculosis treatment success under the DOTS programme in Namibia. *Expert Review of Respiratory Medicine.* 12(11):979.
3. Verbeeck, R. K., Günther, G., **Kibuule, D**., Hunter, C., & Rennie, T. W. (2016). Optimizing treatment outcome of first line anti-tuberculosis drugs: the role of therapeutic drug monitoring. *European journal of clinical pharmacology*, *72*(8), 905-916.
4. **Kibuule D**, #Aises P, Rennie TW, Verbeeck KR, Mubita M (2018). Predictors of Loss to follow-up under the DOTS programme in Namibia. **[Oral abstract]**, *Medicine Utilization Research in Africa (MURIA group), Faculty of Health Sciences University of Namibia, July 2018*

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LIST OF ABBREVIATIONS AND/OR ACRONYMS

ADR	Adverse Drug Reaction
ART	Antiretroviral Therapy
C2h	Concentrations at 2 Hours
CB-DOTS	Community-Based Directly Observed Treatment
CBTBC	Community-Based Tuberculosis Care
CDR	Case Detection Rate
C_{max}	Maximum Drug Concentration
CNR	Case Notification Rate
CPT	Cotrimoxazole Preventive Therapy
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment - Short course (WHO strategy)
DR-TB	Drug-Resistant Tuberculosis
DST	Drug Susceptibility Testing
DS-TB	Drug-Sensitive Tuberculosis
EMB	Ethambutol
EPTB	Extra Pulmonary Tuberculosis
ETR	Electronic Tuberculosis Register
FB-DOT	Facility Based Directly Observed Therapy
FDC	Fixed-Dose Combination
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
INH	Isoniazid
IPT	Isoniazid Preventive Therapy

ITS	Interrupted Time Series Analysis
MDR-TB	Multi-Drug-Resistant Tuberculosis
MoHSS	Ministry of Health and Social Services
MTB	*Mycobacterium tuberculosis*
MTB/Rif pos	Positive for *Mycobacterium* and Rifampicin resistance
MTP	Medium Term Plan for Tuberculosis and Leprosy
NIP	Namibia Institute of Pathology
NSP	New Smear-Positive
NTLP	National Tuberculosis and Leprosy Programme
PTB	Pulmonary Tuberculosis
PZA	Pyrazinamide
RHZE	Rifampicin Isoniazid Pyrazinamide Ethambutol
RMP	Rifampicin
TB	Tuberculosis
TB/HIV	Tuberculosis and Human Immunodeficiency Virus coinfection
TSR	Treatment Success Rate
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis
Xpert	Gene expert resistance testing

ACKNOWLEDGEMENTS

Various persons and institutions have supported this research project. First, I acknowledge the Lord God Almighty, who makes all things possible *"Matthew 19:26. ... "Is anything too difficult for the LORD?"* In addition, this project would not be possible without the countless support of my dear wife, Harriet R. Kagoya, and children, Dannette Najuuko, Hadriel Lubyaayi and Dasha Zalwango. Secondly, I appreciate my research supervisors, Prof. Roger K Verbeeck, Prof Timothy W Rennie and Prof. Ette Ene from whom I have acquired and bettered my scientific approach to research and for the invaluable critique at various stages of design, implementation and reporting. Thirdly, I extend my appreciation to the staff of the National Tuberculosis and Leprosy Programme, Ministry of Health and Social Services, in particular Dr. Ruswa Nunurai, Dr. Farai Mavhunga, Ms. Faustina Amutenya and Ms. Thomas for the guidance in the design and data collection processes. Fourthly, I acknowledge the co-authors particularly my supervisors, Prof, Michael Law and Prof. Brian Godman, among others for appraising the various manuscripts. I acknowledge my research assistants Tafadzwa TE, #Aises P, Shekuhungama A and Mpande R for their tireless assistance in data collection. I acknowledge all research and ethical review boards and patients that gave informed consent to make this study possible. I would like to appreciate the critical appraisal received from the staff of the School of Pharmacy at the various seminars when this work was presented. Lastly, I would like to thank my fellow PhD students, Mr. A. Ishola and Mr. F. Kalemeera for the togetherness, support and teamwork they have extended to me throughout this project.

May the Lord bless you all!

DEDICATION

I would like to dedicate this dissertation to three persons that motivated and inspired me to undertake a doctoral study at times when I felt it was not "necessary. My inspirational father Prof. L.S. Luboobi, Professor of Biomathematics, Makerere University Kampala and visiting Professor at Strathmore University, Nairobi Kenya and to my mother Ms. Margaret Luboobi (late) for the parental care and investing in my education.

My dear wife Harriet R. Kagoya and Children Dannette Najuuko, Hadriel Lubyaayi and Dasha Zalwango for support you always render to me.

Finally, to Mabeti Chisenga my Bachelor of Pharmacy III student who one morning in 2014 through a friend, "challenged" me to embark on PhD studies. This is the main reason I registered for studies in 2015 and will always remember this day.

Lastly, this dissertation is dedicated to all patients afflicted with tuberculosis worldwide in an effort to improve treatment success rates and End TB by 2035.

DECLARATIONS

I, Dan Kibuule, hereby declare that this study is my own work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

…… …… ……

Name of Student **Signature** **Date**

CHAPTER 1: INTRODUCTION

1.1 Burden and control of Tuberculosis

Tuberculosis (TB), is the leading cause of death worldwide from an infectious disease.[1–3] In 2015 alone, the WHO estimated that TB killed about 1.8 million people globally; 95% of these deaths occurred in developing countries such as Namibia. [4] However, TB can be cured [5–8], and the WHO and the UN Sustainable Development Goals (SDGs) for 2030, calls for a 90% reduction in deaths and an 80% reduction in incidence rates by 2030 versus 2015.[9,10] The SDGs use treatment success rates (TSR, i.e. proportion of patients that are cure or complete treatment) and the case detection rate (CDR, i.e the percentage of TB cases notified against the estimated number cases for that year) as yardsticks for the control of TB. In 2017 alone Namibia with an estimated population of 2.3 million notified over 8 800 new infections (i.e. case notification rate (CNR) of 446 cases per 100 000 persons), and 700 deaths from TB-related infections.[11] Indeed, death rates are unacceptably high given that they are preventable and TB treatment has up to 98% cure rate.[8,12]

A major strategy to reduce TB incidence has been Directly Observed Treatment Short-course (DOTS), which was implemented in Namibia in 1995. Directly observed treatment (DOT), i.e. standardized anti-TB drug regimens administered to patients under direct observation, remains a critical strategic goal of DOTS implementation in Namibia.[3,4] since the implementation of the Community-based-DOTS programme in Namibia in 2005, the number of patients completing treatment TB treatment has increased and has improved the treatment success rates from 64% in 2004 to over 85% in 2015.[13–16] However, poor treatment outcomes such as death, loss to follow up and treatment failure

remain common under the DOTS programme in Namibia and in most developing countries.[13,17]

1.1.1 The burden of tuberculosis: an "endemic" disease in Namibia

Though curable, tuberculosis (TB) causes an estimated 1.8 million deaths annually, the second leading cause of death from an infectious disease worldwide.[18,19] The mortality associated with tuberculosis is highest in Africa, where more than half a million people die from the disease every year.[19–21] In 2017, 700 tuberculosis associated deaths were registered in Namibia, a middle income country in southern Africa with a population of 2.3 million people.[22] Moreover, of the 6.3 million cases of TB notified worldwide in 2016, over 90% (5.7 million) were new infections and a third of these new cases were registered in Africa. Namibia, has the fifth highest TB case notification rate (CNR, i.e. number of new TB cases notified in a country per 100 000 population) globally.[23,24]

The high tuberculosis CNR in Namibia has been linked to the HIV epidemic (with a prevalence estimated between, 14% - 17%), resulting in a resurgence of TB since the mid-1980.[25–28] Similarly, the prevalence of HIV co-infection among TB cases in Namibia peaked at 66.9% in 2008 and has declined to 36% in 2016. The case notification rate of all forms of TB in Namibia peaked at 822/ 100 000 population in 2004. This has since declined to 374/ 100 000 cases in 2017.[13,14] Nevertheless, the CNR in Namibia remains above the global target set at less than 300/100,000.[13,27] In some geopolitical regions of Namibia, that is Erongo, Hardap, Karas and Oshikoto, the CNR is estimated to be three times higher than the national estimate (i.e. over 1 000 cases per 100, 000 population).

Thus, the World Health Organisation (WHO) classifies Namibia alongside other southern African countries that is Swaziland, Lesotho and South Africa as high tuberculosis burden settings.[13,24] This is a major public health concern for a country that attained universal coverage of quality Directly Observed Treatment-Short course (DOTS) services across regions in 2015.[13,15,26]

The growing number of drug resistant tuberculosis (DR-TB) cases notified across countries is another major global public health concern.[23,29–31] The WHO estimates over 500, 000 cases of multidrug resistant tuberculosis (i.e. MDR, tuberculosis resistance to two first line anti-tuberculosis drugs, that is rifampicin and isoniazid) annually.[27,31] The annual incidence of MDR tuberculosis in Namibia is at 200 per 100 000 population, and have been notified across all the 34 health districts.[13,32] Of the 326 cases of MDR-TB cases notified in Namibia 2014, 206 were bacteriological confirmed.[13,33] In the same period 6 cases of extremely resistant drug tuberculosis (XDR-TB, i.e. Tuberculosis strains resistant to first line and second line anti-tuberculosis regimens) were reported in Namibia.

In particular, the incidence of drug resistant TB remains high in central business districts of the Khomas, Ohangwena, Oshana, Otjozondjupa, Kavango and Erongo regions of Namibia. Drug-resistant TB is a serious public health issue in low and middle-income countries (LMICs) such as Namibia, as it is difficult and expensive to diagnose and treat successfully. Moreover, the World Health Organisation estimates the treatment success rate for a 2 years regimen for MDR-TB at 49.9%.[24,34]

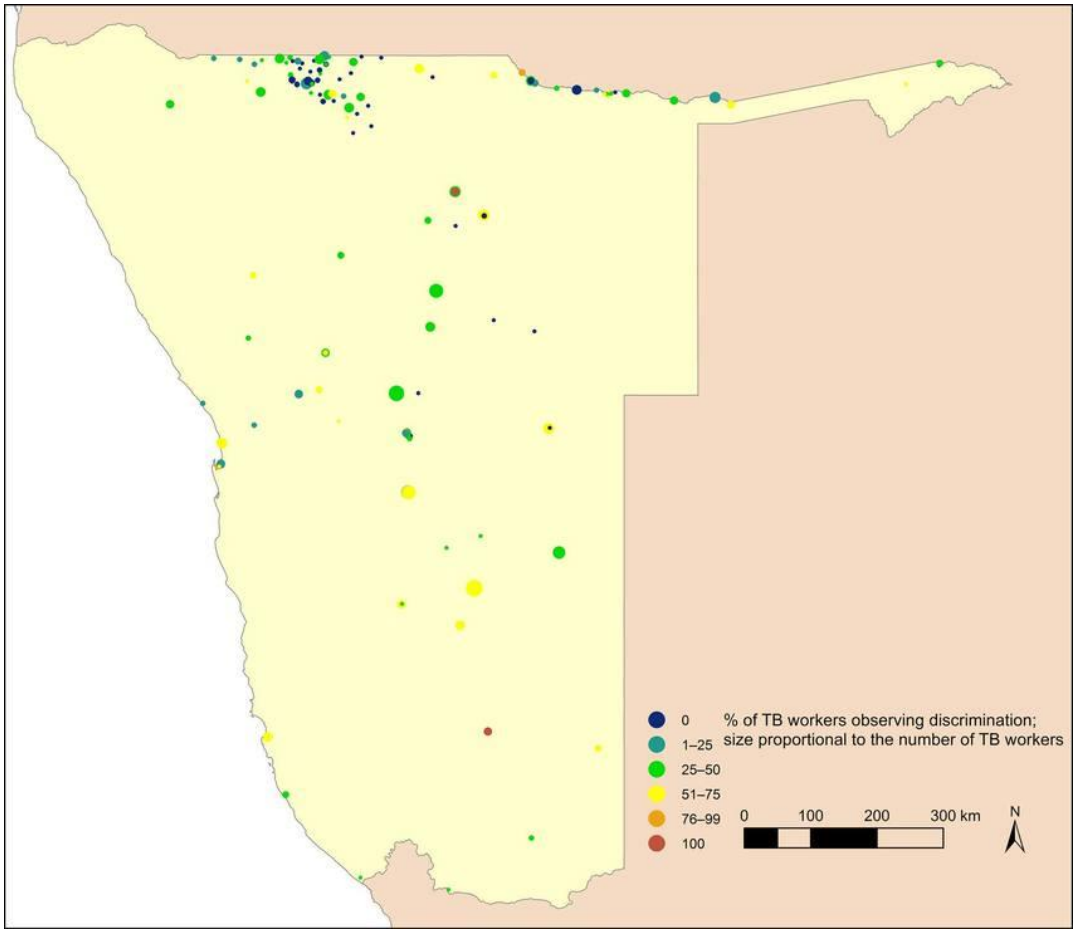


Figure 1. A map of Namibia showing 155 facilities with 741 TB workers". MoHSS, Namibia

TB statistics in Namibia: 5th highest case notification rate in the world, treatment success rate 83% in 2017, Lost to follow-up rate approximately 4% and 700 death due to TB in 2017

1.1.2 The dual burden of Tuberculosis and HIV/AIDS co-infection

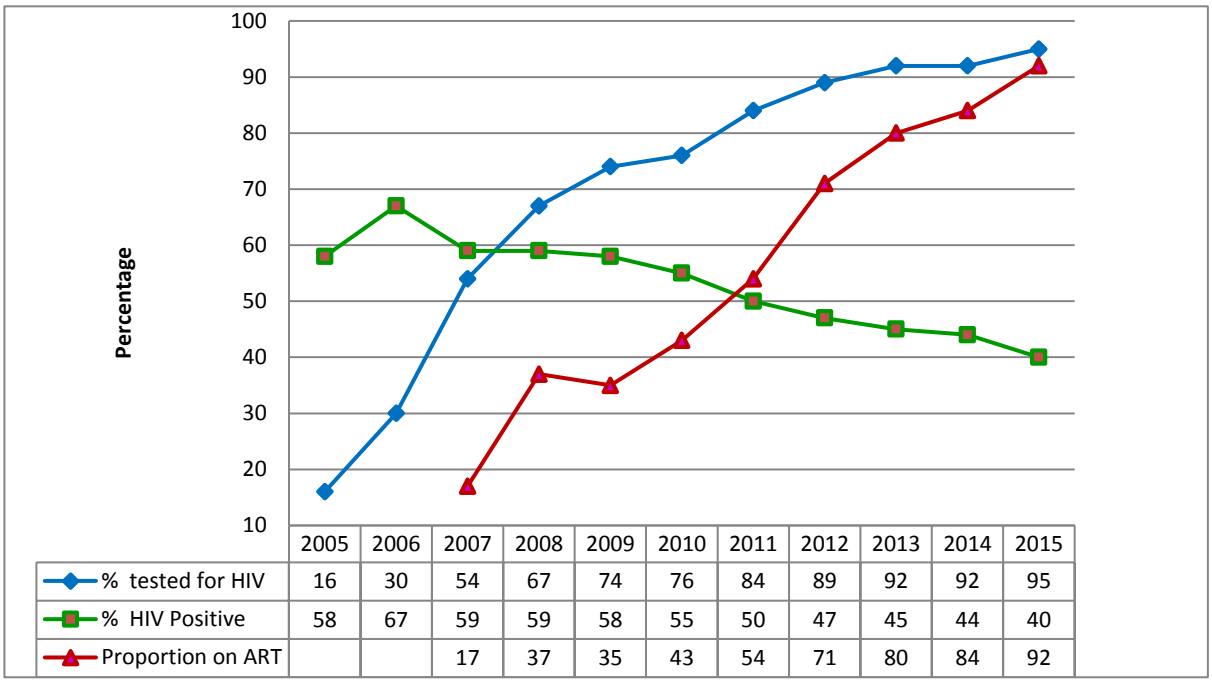
The prevalence of HIV among the 15-49 age group in Namibia is estimated at 13.3%, this is among the highest globally. Indeed, the main driver of the TB epidemics is HIV among

other socio-economic factors (i.e. poverty, poor housing infrastructure) as well as health systems. For instance, the highest TB case notification rates (i.e. 1,410/100,000) in Southern Africa observed in 2000 were attributed to the peak in of HIV epidemic in that region.[23,35]

The National Development Plan of Namibia identifies the control of TB and HIV, as critical to improving health indicators for the country. The burden of HIV co-infection is estimated between 35% and 75% among TB patients living in sub-Saharan countries. Moreover, TB is the main cause of mortality among people living with HIV/AIDS (PLWHA) and a significant driver of the tuberculosis epidemic in Namibia. Nevertheless, the HIV prevalence among TB cases which peaked in 2006 (67%) has declined steadily to 40% in 2015.

Another, challenge is the dual treatment with HIV and TB medication predisposes patients to serious adverse drug reactions such as IRIS, hepatotoxicity and drug-drug interactions. Several studies have reported the occurrence of life-threatening IRIS and hepatotoxicity among patients on co-treatment with first-line ART and anti-TB medication.[1,36] Several, studies report the interaction between rifampicin lowers the plasma levels antiretroviral drugs such as efavirenz, this is a concern as it leads to poor treatment outcomes.[13,37,38] The WHO's test and treat strategy has increased the access to ART and IPT (Isoniazid prophylaxis) among patients with TB and HIV respectively. The ART coverage in Namibia was estimated at 91% in 2012.

Under the test and treat strategy in Namibia, all patients diagnosed with HIV regardless of CD4 counts or co-infection with TB are initiated on ART. However, of concern is the lack of integration of TB/HIV services in order to optimize service delivery and treatment outcomes among this population. In Namibia, TB/HIV co-infected patients should readily access to co-trimoxazole preventive therapy (CPT) and antiretroviral treatment (ART) consistent with national guidelines for the management of TB and HIV.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
% tested for HIV	16	30	54	67	74	76	84	89	92	92	95
% HIV Positive	58	67	59	59	58	55	50	47	45	44	40
Proportion on ART			17	37	35	43	54	71	80	84	92

Figure 2. Trend on coverage of HIV care services for TB patients, 2005-2015; Namibia (Adopted from the NTLP report 2018)

1.1.3 The global strategy to end Tuberculosis (TB)

The World Health Organisation (WHO) aims to "end" tuberculosis globally by 2035.[27,39] An optimal treatment success rate (i.e. the sum total of cure and treatment completion rate) of more than 90% and case identification rate of more than 80%, among others are the main goals in the global end TB strategy as well as the Millennium Development Goals (MDGs).[40] Similarly, Namibia's Medium-Term Plan (MTP I and II) for tuberculosis adopted the treatment success rate target (i.e. 90%), among other goals of the global End TB strategy within its TB programmes.[41,42]

The universal access to Directly Observed Treatment – Short course (DOTS) is the main strategic intervention of the end TB strategy to improve treatment success rates (TSR) across countries.[43] Therefore in 2005 the National Tuberculosis Control Programme (NTCP) scaled up the access to community-based DOTS (CB-DOTS) and universal access to quality DOTS across the geopolitical regions was achieved in 2015.[1,13,41] The roll out of CB-DOTS has markedly improved treatment success rates in Namibia, from 64% in 2004 to about 87% in 2015. Similarly, the rate of loss to follow-up of TB cases declined dramatically from 17% in 2000 to 5% in 2012. [14,44] The death rate among patients on DOTS was estimated at 7%. Nevertheless, the treatment success rates for TB have remained below the 90% global threshold since the implementation of the Community-based DOTS (CB-DOTS) programme in 2005.

Moreover, despite the efforts to end TB in Namibia the treatment success rate has since declined from 87% in 2016 to 83% in 2017.[26] Consequently, the aim of the current study was to develop a model for optimizing tuberculosis treatment success rates in Namibia, a country that achieved universal coverage of DOTS services.

The direct observation of administration of TB treatment (i.e. DOT, Directly Observed Treatment) is a critical intervention under the DOTS strategy to improve tuberculosis treatment success rates.[6,45] The DOT regimens for tuberculosis are fixed dose combinations (i.e. FDC, a combination of four TB medications in one or two tablet(s)/capsule(s) to facilitate easy administration and adherence) of four first line anti-tuberculosis medicines, rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol

(E).[44,46] The DOT is administered over six months in two phases (i.e. two months intensive with RHZE and four months continuation phase with RHE) to optimize tuberculosis cure rates of up to 99%.[6,44]

Additionally, the FDC directly observed treatment provide synergistic effects by killing active, semi-dormant and dormant as well as intra or extra-cellular bacilli. Nevertheless, the treatment success rates (i.e. the sum total of cases who are cured and those who completed treatment) in most Low- and middle-income countries for drug sensitive TB remain below the global target of 90%.[47] The global tuberculosis treatment success rate (TSR, i.e. sum total of cure rates of new smear positive cases of tuberculosis in patients who complete a full course of treatment) is 86% in 2012, and 81% in the African region.[25,44] In Namibia, the TSR for new smear positive TB cases improved from 75% in 2007, to 76% in 2008, 85% in 2009 to 85% in 2012 and 87% in 2013.[25,44]

1.2 Determinants of Tuberculosis treatment success rates (TSR)

Despite the universal access to quality DOTS services in Namibia, poor treatment outcomes (i.e. failure, death, loss to follow-up) remain common among TB cases with drug sensitive tuberculosis.[41,44] In general, the main factors attributed with the sub-optimal treatment success rates in the LMIC have been HIV coinfection[36,48,49], limited access to quality DOTS services,[13,16] and adherence to treatment,[29,36,50] among others. The non-adherence has been partly linked to high incidence of adverse drug effects associated with all the four medicines in the DOT regimen.[51–53]

Moreover, the use of FDC regimens tuberculosis is associated with life-threatening adverse reactions such as drug-induced hepatitis and hypersensitivity reactions with RHZE and optic neuritis and renal failure with ethambutol, among others.[54–56] Despite this, the burden, determinants and impact of adverse drug reactions on treatment success rates have not systematically assessed among cases on first line DOT regimens following universal access to DOT regimens across regions in Namibia in 2015.[57]

The determinants of the sub-optimal tuberculosis treatment success rates, remain complex and their impact varies across countries and/or populations.[47,58,59] Consequently, the aim of the study was to comprehensively model the impact of population, patient and TB drug – related determinants on treatment success in a high TB burden setting.

1.2.1 Population and patient level determinants of treatment success rates

There is limited data on the impact of population and patient level determinants on TB treatment success rates in Namibia. For instance, in Namibia treatment failure is mainly attributed to the high treatment default rates (i.e. patients lost to follow-up after initiating treatment), which was estimated at 17% in 2000 and 5% in 2012. Health system weaknesses, lack of effective regimens, treatment challenges and drug resistant tuberculosis are among other factors linked with sub-optimal tuberculosis cure rates.[23]

Furthermore, several studies have attributed poor treatment success rates to sub-therapeutic plasma levels of first line fixed dose combinations (FDC) standard regimens

for tuberculosis.[60–62] Peloquin *et al.,* describe the optimal therapeutic serum concentrations of antituberculosis drugs to achieve high treatment success rates as: 2 – 6 µg/l for isoniazid, 8 – 24 µg/l for rifampicin, 3 – 6 µg/l for ethambutol and 20 – 60 µg/l for pyrazinamide.[63,64] Among patient level determinants of sub-therapeutic plasma concentrations of anti-tuberculosis medications is HIV infection, gastrointestinal tract disorders, high body weight, male gender or diabetes mellitus. [65–67]

McIlleron *et al.,* showed that TB cases with HIV co-infection had a 39% and 27% reduction in plasma concentrations of rifampicin and ethambutol respectively. [68,69] The impact of weight on serum levels of anti-TB drugs is particularly important, when standard doses (i.e. mg/kg) are used for first-line drugs, where patients with low weight are likely to have lower levels[70,71] The McIlleron *et al.,* and other studies also identify dosage formulation, the female gender, old age, previous exposure to anti-tuberculosis treatment and dose determination (i.e. weight-band dosing) as risk factors for sub-therapeutic plasma concentrations of some or all four first line TB drugs.[68,69,72,73] The role of patient level –risk factors including extent of cavitation, time to presentation, the TB diagnosis (i.e. pulmonary vs extra pulmonary, drug sensitive vs drug resistant) and treatment regimen impact on serum concentrations of TB medication and/or treatment success rates.[69,74,75]

Another important factor is the genetic polymorphism in metabolism of isoniazid, one of the most potent first line anti-tuberculosis medicines. Several studies in particular that of Burhan *et al* report a significantly lower plasma concentration at 2 hours (C2h) for

isoniazid among cases with a fast acetylators phenotype (0.9 µg/l) compared to the slow (2.2 µg/l) (p <0.001). [46,76,77] Moreover, any isoniazid dose reduction below 6 mg/kg body weight significantly reduces plasma levels of isoniazid among the faster acetylators. On the other hand, slow acetylators require only a 3 mg/kg dose to achieve therapeutic concentrations for isoniazid.[78] Similarly, low TB drug concentrations have been linked to drug-drug interactions, particularly with efavirenz, a non-nucleoside reverse transcriptase inhibitor widely in first-line antiretroviral therapy (ART). A study by Naidoo *et al.* showed that Efavirenz (EFV) reduces moxifloxacin plasma exposure. [79–82] Chirehwa *et al*., also demonstrated EFV lowers the drug exposures for isoniazid among the rapid acetylators.[83,84]

1.2.2 Prevalence of sub-therapeutic plasma levels of Tuberculosis medication

Studies estimate the prevalence of sub-therapeutic plasma levels for at least one first line anti-tuberculosis drug (RHZE, i.e. rifampicin, isoniazid, pyrazinamide and ethambutol) to range between, 35% to 90% across populations.[60,61,66,76,85,86] For instance, a study by Burhan *et al*., among Indonesian TB patients, recorded a 91% prevalence of sub-therapeutic concentrations at 2 hours (C2h) of isoniazid, rifampicin, or pyrazinamide; and 60% had at least two low concentrations at 2 hours. [76] In a study by Fahimi *et al.,* among TB patients in Iran, 81% of the patients had drug plasma concentrations lower than the target ranges for at least one administered drug.[87] The median peak plasma concentrations of isoniazid, rifampicin and pyrazinamide were respectively 2.5, 4.0 and 43.6 µg/l, and the prevalence of low concentrations of H, R and Z was 49.1%, 92.5% and 8.7% for the respective drugs.

A study by Verhagen *et al.*, among children below the age of 16 years, 25 patients (83%) had an isoniazid Cmax below 3 μg/l and 23 patients (77%) had a rifampicin Cmax below 8 mg/l.[88] One patient (3%) had a pyrazinamide Cmax below 20 μg/l. A study by Um *et al.*, also showed that out of the 69 patients, 46.4% had serum 2h concentrations of at least one TB medicine below reference levels. The prevalence of low serum concentrations of RHZE were 23.5%, 15.2%, 22.4% and 4.5%, respectively.[60] In a study by Tappero *et al.*, among 91 patients in Botswana with pulmonary TB, the plasma levels were low for isoniazid, (30%) rifampicin (78%) , ethambutol, (41%) of 91; and pyrazinamide (1%)[89]. Low serum concentrations of both isoniazid and rifampicin occurred in 23 (26%) of 90 patients. Heysell *et al.*, through a retrospective cohort analysis showed that 22 patients had concentrations lower than the expected range for rifampicin, 23 of 39 patients had low levels of isoniazid, and 8 of 26 patients had low levels of ethambutol; all 20 patients tested for pyrazinamide were within expected range. [90]

Another study by Holand *et al*., studied pharmacokinetics among patients with TB and advanced HIV infections: of the 21 patients, 18 (86%) had low serum concentrations of at least one drug 2 hours after ingestion: 2 (10%) had low isoniazid concentrations, 5 (24%) had low rifampicin concentrations, and 11 (52%) had low serum concentrations of both drugs. The median number of dosage adjustments to attain normal concentrations was 1 (range 0–4 adjustments). In a study by Kayhan and Akgünes, among 49 enrolled active pulmonary tuberculosis patients, the prevalence of a low concentration of isoniazid, rifampicin, ethambutol and pyrazinamide were 28.6, 75.5, 18.4 and 20.4%, respectively. [91]

1.2.3 Impact of sub-therapeutic levels on Tuberculosis treatment success

Of concern is the extremely wide variability in drug concentrations reported across studies, particularly for rifampicin.[92] The wide variability in the pharmacokinetic studies is attributed to the quality of the formulation and the assay methodology; amongst all the patient, genetic, disease and environmental factors.[92]

There is conflicting evidence on the impact of sub-therapeutic plasma concentrations of first line antituberculosis drugs on treatment success, particularly among patients with an HIV coinfection.[60,76,93–95] This is particularly important in the African context, where the prevalence of HIV coinfection is high. Whilst, some studies report significant associations between low concentrations of anti-TB drugs and poor treatment response[76,94,96–99] other studies found no association between plasma levels and the treatment response determined by an 8 weeks of culture conversion. [58, 74]

1.3 Aim and objectives of the thesis

Consequently, the main aim of this thesis was to develop a model(s) for optimizing tuberculosis treatment success rates in Namibia based on the impact of population-level time varying covariates (i.e. health or programmatic indicators/characteristics of the Namibian population that change with time, such as HIV prevalence and DOTS coverage) as well as, patient-level and tuberculosis treatment regimen (i.e. first line DOT regimen) covariates. The specific population, patient and drug level statistical models for predictors of TB treatment success rates will be translated into a conceptual model for policy development to optimize treatment outcomes in DOTS programmes in Namibia and similar settings. Specifically, the thesis aimed to address four research questions:

(i) What is the impact of the DOTS programme, and population-level time varying covariates on treatment success rates in Namibia?

(ii) What patient/clinical level covariates significantly affect TB treatment success rates in Namibia?

(iii) What is the impact of HIV coinfection on the serum levels (Cmax) of first line anti-tuberculosis medicines in the African population?

(iv) What is the burden of adverse drug reactions among patients initiated on first line DOT regimens in Namibia?

Ultimately, a model based on population, patient and tuberculosis drug predictions was developed to provide strategic and policy guidance for optimizing treatment success rates in Namibia.

1.4 Thesis overview and scope

The scope of the thesis is to develop a policy and/or practice model to optimize tuberculosis treatment success rates in Namibia. This required the assessment of the effectiveness of the current interventions to improve treatment outcomes as well as determine the interplay of predictors of treatment success rates at three levels that is population level, patient/clinical level and drug product level. Thus the thesis is organized in nine main chapters depicting population, patient and drug level dynamics of treatment success rates and general introduction and discussion sections.

Chapter 1, i.e. the general introduction provides a background to the burden of different forms of tuberculosis, TB/HIV coinfection and sub-optimal treatment success rates from

a global, regional and Namibia perspective. Indeed, the chapter depicts TB as a leading cause of mortality and public health concern globally, where Namibia is ranked fifth among high TB burden countries. The chapter also highlights the current burden of sub-optimal treatment success rates in most developing countries including Namibia despite the scale of high quality DOTS programmes.

Chapter 2 is a literature review of the current evidence on effectiveness of DOTS programmes on TSR worldwide as well as the impact of population, patient and drug level predictors of treatment success rates. In addition, detailed literature review is covered under the introduction and discussion sections of the respective chapters. Chapter 3 aimed to describe predictive models of the effectiveness (i.e. changes in the level and trend in treatment success rates) of the current community-based DOTS programme on TB treatment success, cure and treatment completion rates in Namibia that aims to "end" TB by 2035.

Predictive models were developed for treatment success rates (i.e. sum total of the cure and treatment completion rates) for patients with drug sensitive tuberculosis (i.e. new smear positive, retreatment cases and smear negative cases) as well as drug resistant cases using interrupted time series (ITS) analysis. In addition, we modeled the impact of various population-level covariates (e.g. prevalence of HIV, access to DOTS services and antiretroviral (ARV) treatment as well as tuberculosis resistance patterns, among others on trends of tuberculosis treatment success rates in Namibia.

Secondly, Chapter 4 to 6 aimed to identify the patient-level predictors of three key tuberculosis treatment outcomes, i.e. treatment success rates (TSR), loss to follow-up and case-fatality rates using regression modelling. Thus the patient level predictors of TSR are presented in chapters, i.e. Chapter 4, 5 and 6 to represent the respective studies. Chapter 4 describes a statistical model for independent predictors of TB treatment success rate under the DOTS programme in Namibia. Chapter 5 describes a model for patient level predictors of loss to follow-up of TB cases under the DOTS programme in Namibia. Chapter 6, describes two sub-studies using hospital-based data and a nationawide database modelled patient-level predictors of tuberculosis case-fatality under the DOTS programme in Namibia. The predictors in the three studies provide insights on programmatic, clinical and/or patient related gaps in the current DOTS programme that require strengthening.

Thirdly, Chapter 7 and 8 cover two studies, one focusing on the pharmacokinetic (Chapter 7), and other pharmacovigilance (Chapter 8), aspects of the first line DOT regimens that are widely reported to impact on TB treatment outcomes. In Chapter 7, models of the effect of HIV on the maximum serum-levels (C_{max}) of the four first line DOT medicines in the African population were deduced. In this Chapter, we performed a metanalysis to assess the impact of HIV/AIDS on serum levels of first line anti-tuberculosis drugs with focus on Africa, a region with the greatest burden of the disease. There is conflicting data on the impact of HIV on serum levels and/or treatment success rates in the African population. In Chapter 8 we describe the pharmacovigilance (i.e. burden of adverse drug reactions among patients on first line DOTS) considerations of the WHO recommended

Fixed Dose Combination DOT first line regimens in Namibia compared to global rates. Two studies, a systematic review and an exploratory hospital-based studies were conducted to estimate the burden (i.e. incidence, types and grades) and describes the factors associated with adverse drug reactions among patients initiated on first line tuberculosis DOT regimens globally and in Namibia.

The concluding chapter (Chapter 9) discusses a consolidated model that provides a policy/practice frame work for optimizing treatment success rates in Namibia and related settings. This final model synthesis of the interrelationship of the six studies, i.e. Chapter 3 through to 8 and aggregates population, patient and drug product related predictors of treatment success rates to harness the current progress, gaps and propose future interventions. The model thus outlines strategic recommendations based on findings in the preceding Chapters, i.e. 3 through 8, based on population-level, patent-level and/or drug level models.

1.5 Research setting

The research setting is Namibia, that is tuberculosis and leprosy Programme at community, district, regional and national levels. Namibia an upper-middle income country located in southwest Africa gained independence in 1990. The country has a surface area of 824,295 km^2 and a population of 2,113,077, the least densely populated country in the world. The country is divided into 14 geopolitical regions, with the capital city Windhoek in the Khomas region. The life expectancy is estimated at 67 years. Most

of the population (57%) lives in communal and commercial farming compared to urban (43%) settings. A significant proportion of the population (26.9%) live below the poverty line, and depend on subsistence farming as the main source of livelihood. The majority of the population (60%) lives in the northern part of the country. The sparse distribution of its population (i.e. 2.6 people per square meter) is an important barrier to access to services, including primary health care services.

Namibia's health care delivery is based primary health care (PHC) system. The National Development Plan recognizes TB, HIV and malaria as priority diseases. The delivery of health services is integrated at the national, regional, district and community levels. The administration of health services is decentralised to 14 regional health directorates and 35 health districts. The public health facilities comprise of 1,150 outreach points, 267 clinics, 44 health centres, 32 district hospitals, 3 intermediate hospitals and 1 national referral hospital, as well as various social welfare service points (Table 1).

In Namibia, TB is among the three most frequent causes of hospitalization and reasons for attendance in the outpatient clinics. Namibia alongside Swaziland, Lesotho, and South Africa have the highest estimated per capita burden of tuberculosis in the world.

Table 1: Distribution of hospitals, clinics and laboratories in Namibia

Region	Projected Population (2017)	Number of Hospitals	Number of Health Centres	Number of Clinics	Labs with TB smear microscopy
//Kharas	87,460	3	3	13	3
Erongo	189,014	6	2	15	3
Hardap	88,743	2	3	11	2
Kavango East and Kavango West	240,767	4	7	46	4
Khomas	431,247	5	2	7	1
Kunene	100,157	3	3	22	3
Ohangwena	257,784	3	2	28	3
Omaheke	75,191	1	1	12	1
Omusati	251,369	4	6	41	4
Oshana	191,898	2	5	11	1
Oshikoto	197,901	3	3	16	2
Otjozondjupa	156,309	6	3	20	4
Zambezi	100,547	1	4	25	1
National	**2,368,747**	**43**	**44**	**267**	**32**

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CHAPTER 2: LITERATURE REVIEW

2.1 Search strategy

A literature review of studies published in English upto May 2018, that had assessed effectiveness of DOTS programme, or predictors of tuberculosis treatment outcomes or pharmacokinetics of first-line anti-tuberculosis medicines and safety of DOT regimens was conducted separately for each study. The search strategy detailed applied search terms unique to each study (reported under each study for systematic reviews). Boolean operators such as AND, OR and NOT, with extensions * and wt., were used alongside the synonyms for the key terms to focus the search. For instance, the search strategy employed for the pharmacokinetic study was (pharmacokinetics) AND (rifampicin OR isoniazid OR pyrazinamide OR ethambutol) AND (tuberculosis) AND (the African countries specific search term). The search strategies were applied in search engines or databases that included Mendeley, PubMed, EMBASE, Google scholar, Cinahl, Cochrane library, Scopus, African Journals Online and the reference lists of retrieved articles were also reviewed to identify other studies in gray literature.

2.2 Effectiveness of the community-based DOTS programme on TSR

Tuberculosis can be cured [1–4], and the WHO and the UN Sustainable Development Goals (SDGs) for 2030, calls for a 90% reduction in deaths and an 80% reduction in incidence rates by 2030 versus 2015.[5,6] Global initiatives have expanded DOTS (i.e Directly Observed Therapy Short-course strategy) services and markedly improved CDR and TSR in Lower and Middle Income Countries (LMIC) including Namibia.[7–11] Despite the 100% scale-up of high quality and community-based Directly Observed Treatment (DOT),

Namibia still falls short of the national and global targets for TSR of 95%.[9,12] Recent analysis suggests that TSR in Namibia have reached a maximum of less than 95% global bench mark, and improvements have been marginal in the past decade. [7,11,13] The TSR are even lower among the retreatment and smear negative cases. [14] [9] The sub-optimal treatment success rates are thus a major concern towards eliminating TB in Namibia. Moreover, stagnation in TSR in Namibia in the past decade (2004-2015), coincides with the rising burden of drug resistant tuberculosis (DR-TB).[15] Evidence in Namibia and other LMICs suggests that current DOTS strategies are not comprehensive enough to "End TB" by 2035. [7,16–21]

2.3 Predictors of tuberculosis treatment success rates

Recent analysis suggests that TSR in Namibia have reached a maximum of less than 95% global benchmark, and improvements have been marginal in the past decade. [7,11,13] The TSR are even lower among the retreatment and smear negative cases. [14] [9] The sub-optimal treatment success rates are thus a major concern towards eliminating TB in Namibia. Moreover, stagnation in TSR in Namibia in the past decade (2004-2015), coincides with the rising burden of drug resistant tuberculosis (DR-TB).[15] Evidence in Namibia and other LMICs suggests that current DOTS strategies are not comprehensive enough to "End TB" by 2035. [7,16–21] Studies in other low and middle-income countries (LMICs) such as India and Malaysia estimate higher incidences of LTFU, 19.2% and 24% respectively. [22,23] In addition, LTFU is an important risk factor for re-emergence of TB strains resistant to first line anti-tuberculosis drugs.[24]

2.4 Predictors of loss-to follow up under the DOTS programme

The universal access to community-based TB care through the Stop-TB and End-TB strategies implemented since 2005 has improved case identification and treatment outcomes in Namibia.[7] Nevertheless, the gradual rise in incidence of drug resistant TB (DR-TB) and poor treatment outcomes such as 'lost-to-follow-up' (LTFU, i.e. an interruption of TB treatment for at least 2 consecutive months) and death [7,11,25,26] are major barriers to ending TB in Namibia. [27–30] For instance, the incidence of LTFU among notified cases in Namibia increased from 4% in 2014 to 10% in 2015. Studies in other low and middle-income countries (LMICs) such as India and Malaysia estimate higher incidences of LTFU, 19.2% and 24% respectively. [22,23]

In addition, LTFU is an important risk factor for re-emergence of TB strains resistant to first line anti-tuberculosis drugs.[24] In 2014, an estimated 300 000 cases of multi-drug resistant tuberculosis (MDR-TB, i.e. resistance to backbone first line anti-TB medicines, rifampicin and isoniazid) were notified globally.[13] In the same year Namibia notified 137 MDR-TB and 6 extensively-drug resistant tuberculosis (XDR-TB, i.e. MDR-TB with resistance to second line TB drugs, aminoglycosides and/or fluoroquinolones) cases. [9] The significance of risk factors of LTFU, i.e. patient demographics, socio-economic status, DOTS programme, clinical covariates, TB treatment regimen and HIV co-infection on LTFU have been contested across countries. [14,15,18-25]

2.5 Predictors of tuberculosis case fatality

The World Health Organisation (WHO) estimated about 9.6 million new cases of TB globally, that led to 1.8 million death in 2016.[12,13] A significant number of the TB

associated deaths (0.4 million) were among patients with co-infected with HIV. [31] Moreover, 21% of the new cases notified (i.e. 281 cases per 100,000 population) were from the African region, and is more than double the global average (i.e. 133 cases per 100,000 population).[24] In 2017 alone Namibia with an estimated population of 2.3 million notified over 8 800 new infections (i.e. case notification rate (CNR) of 446 cases per 100 000 persons), and 700 deaths from TB-related infections.[32] Indeed, death rates are unacceptably high given that they are preventable and TB treatment has up to 98% cure rate.[4,33] Since the implementation of the Millennium Development Goals (MDGs), the TB incidence has declined by 18% world-wide and has prevented an estimated 4.6-6.3 million TB related death. [31,34–36]

HIV co-infection among TB patients is linked to poor prognostic outcomes including death, particularly among patients in low and middle-income countries (LMICs). [4,31,37] This is a major concern given that over 38% of TB patients in Namibia have HIV co-infection, and is among the highest globally [38] . Also, the death rate among TB patients varies widely among the 14 geographical regions of Namibia, with the Khomas region (i.e. capital region of Namibia) and Kavango region (i.e. region with highest poverty rates in Namibia) the most affected.[38,39] The impact of clinical, patient socio-demographic[39], programmatic and treatment factors on death rates among TB patients on the under DOTS in Namibia. [31,40] The current high death rate among patients on the DOTS programme in Namibia may stigmatize patients and/or communities, reduce adherence to treatment, and affect negatively the health seeking behaviours and treatment and public health outcomes.[24,41,42]

2.6 Pharmacokinetics of first-line antituberculosis drugs

At least one-third of people living with HIV/AIDS (PLWHA) globally are co-infected with TB [2] and TB remains the major cause of hospitalization and death among PLWHA. However in the sub-Saharan region, AIDS-related mortality reduced by 45% between 2005 and 2015.[43] This reduction has been attributed to increased access to antiretroviral therapy (ART) and Directly Observed Treatment-Short course (DOTS) programmes as well as the integration and strengthening HIV and TB health care services particularly in primary health care.[44–46] Several studies attribute poor TB treatment outcomes to sub-therapeutic serum levels of anti-tuberculosis medicines, especially among patients co-infected with HIV among other factors. [47–51]

For instance, studies have shown plasma levels of rifampicin to be below target concentrations (i.e. <8µg/mL) in up to 75% of patients.[52–55] On the other hand, some studies show no significant relationship between HIV coinfection and serum levels of first-line TB medication,[52,56–59] and/or tuberculosis treatment outcomes.[60] The interplay between TB/HIV disease severity and other patient factors such as age[61,62], comorbidities[63], sex and pharmacogenetics[64–66] has not been systematically reviewed in the sub-Saharan population. Furthermore, there are conflicting reports on the relationship between sub-optimal serum levels of first-line anti-tuberculosis treatment with treatment outcomes.[67] Indeed, knowledge on the effect of HIV/AIDS on pharmacokinetics of TB medication would provide direction on the appropriate dosage adjustments and improve treatment outcomes.

2.7 Prevalence of adverse drug reaction of anti-tuberculosis drugs

Since the implementation of the CB-DOTS programme in Namibia in 2005, the number of patients completing treatment TB treatment has increased and has improved the treatment success rates from 64% in 2004 to over 85% in 2015.[7,9,17,68] However, poor treatment outcomes such as death, loss to follow up and treatment failure remain common under the DOTS programme in Namibia and in most developing countries.[9,27] The poor treatment outcomes are partly attributed to non-adherence to TB treatment due to mild and/or life-threatening adverse effects.[69–72]

There is growing evidence that adverse reactions (ADRs) associated with TB-medication are a risk factor to adherence to treatment and poor outcomes such as death and loss to folow-up.[70,73–76] Moreover, severe adverse reactions such as drug-induced hepatotoxicity[77,78] cutaneous reactions and neuropathies often lead to interruption of treatment with first line treatments.

A study in Nepal reports that ADRs account for 5 % of all hospital admissions and caused death in 0.1% of TB cases .[79,80] Moreover, a survey in Namibia by Sagwa *et al.* (2012) on ADRs among TB patients on second line-DOTS regimens found the occurrence of tinnitus at 45% versus lower rates reported in literature (5.1% - 24%) and for hearing loss (25% vs range: 6.7% - 33%).[73] As a result, adverse drug reactions associated with DOTS regimens cause significant morbidity and impede treatment success.[73,81–87] The risk factors ADRs for first line DOTS treatment have been contested across studies; which include liver disease, HIV or hepatitis C coinfections, drug regimen, and intensive phase, alcohol

intake, female sex, ethnicity, drug abuse and nutritional status.[83,88–91] Consequently, the aim of the study was to assess the occurrence of DOTS associated ADRs in Namibia to provide guidance on case management.

2.8 Gaps in current literature

However, there are conflicting reports on the impact of DOTS intervention and risk-factors for tuberculosis treatment outcomes across populations, particularly pharmacokinetic variability, socio-demographic and baseline clinical characteristics. [92–94] To date, the magnitude and impact of these risk factors on treatment outcomes has not been systematically evaluated in Namibian and other LMIC where the burden of TB remains high.[5, 14, 15, 18-25]

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CHAPTER 3: POPULATION LEVEL MODELING OF TREATMENT SUCCESS RATES IN NAMIBIA

Effectiveness of the community-based DOTS strategy on tuberculosis treatment success rates in Namibia

Published: *International Journal of Tuberculosis and Lung Disease*, Apr 1; 23(4):441-9

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3.1 Abstract

Setting: Directly Observed Treatment Short-course is a key pillar of the global strategy to end tuberculosis.

Objective: The effectiveness of community-based compared to facility-based DOTS on tuberculosis treatment success rates in Namibia was assessed.

Methods: Annual tuberculosis treatment success, cure, completion and case notification rates were compared between 1996 and 2015 by interrupted time series analysis. The intervention was the upgrading by the Namibian government of the tuberculosis treatment strategy from facility-based to community-based DOTS in 2005.

Results: The mean annual treatment success rate during the pre-intervention period was 58.9% (range: 46-66%) and significantly increased to 81.3% (range: 69-87%) during the post-intervention period. Before the intervention, there was a non-significant increase (0.3%/year) in the annual treatment success rate. After the intervention, the annual treatment success rate increased abruptly by 12.9% ($p < 0.001$) and continued to increase by 1.1%/year thereafter. The treatment success rate seemed to have stagnated at approximately 85% at the end of the observation period.

Conclusion: Expanding facility-based DOTS to community-based DOTS significantly increased the annual treatment success rates. However, the treatment success rate at the end of the observation period had stagnated below the targeted 95% success rate.

KEY WORDS: IMPACT, DOTS, TREATMENT SUCCESS RATES, NAMIBIA

3.2 Introduction

Tuberculosis (TB) remains a significant health problem in many lower and middle-income countries. In 2015, there were 10.4 million cases of TB worldwide, leading to an estimated 1.8 million fatalities.[1] The disease is particularly prevalent in Sub-Saharan African countries such as Namibia, where the case notification rate (CNR, i.e. the number of new and relapse TB cases notified in a year) was 489 cases per 100,000 people in 2015.[2] A major strategy to reduce TB incidence has been Directly Observed Treatment Short-course (DOTS), which was implemented in Namibia in 1995. Directly observed treatment (DOT), i.e. standardized anti-TB drug regimens administered to patients under direct observation, remains a critical strategic goal of DOTS implementation in Namibia.[3,4]

TB case identification and optimization of treatment outcomes through DOTS are the key global strategies to "end TB" in Namibia by 2035.[1,4] Unsuccessful treatment outcomes however, are important risk factors for the development of drug-resistant TB, a condition that is extremely difficult and expensive to treat.[5-9] In the past decade the community-based DOTS has improved treatment outcomes globally and in Namibia.[9,10] Nevertheless, Namibia, an upper-middle income country in southern Africa with a population of 2.2 million, remains one of the countries with the highest incidence of TB in the world.[1,2,10] Therefore, facility-based DOTS (FB-DOTS) was scaled-up to all public health facilities in Namibia between 1991-1995 as a strategy to control TB and to improve treatment outcomes. [10, 11]

In Namibia, FB-DOTS refers to when directly observed therapy and related services were only accessible at a health facility before 2005, and CB-DOTS is when DOTS services

were extended to villages and households through community-based health workers. An assessment of the FB-DOTS strategy in Namibia in 2002 showed that, since its introduction in 1991-1995, TB incidence rates had not declined and treatment success rate (TSR, i.e. the proportion of cases cured or completed TB treatment in a given year) was at its lowest in 2004.[10] As a result, the facility-based DOTS was scaled-up to community-based DOTS (CB-DOTS) under the first national TB and Leprosy Medium Term Plan I (MTP-I) implemented from 2004 - 2009.[12] The access to high quality CB-DOTS was further expanded, i.e. to all regions, public-private workplaces and integrated with community-based HIV (Human Immunodeficiency Virus) care and enhanced i.e. improved quality of bacteriological assessments and the standardization of DOTS services such as treatment, DOT support, among others under MTP-II (2010-2016) to empower DOT supporters within each community to deliver quality DOT services.[13,14] The targets for treatment success rate under MTP-I and MTP-II were 85% and 90%, respectively.[12,13]

With the implementation of MTP-I in 2004, an electronic TB data base was started to closely monitor treatment outcomes. The objective of this study was to use the annual rates of treatment success, cure, treatment completion, before (1996-2004) and after (2005-2015) the implementation of MTP, to assess the effectiveness of CB-DOTS to improve TB treatment outcomes.

3.3 Methods

3.3.1 Facility-based and community-based DOTS in Namibia

A comprehensive description of the implementation of facility-based DOTS in Namibia and the scale-up to community-based DOTS under the first and second National TB and Leprosy Medium Term Plans (MTP-I) and MTP-II) can be found below.

Namibia achieved a countrywide DOTS coverage at all public health facilities that is 42 hospitals, 34 health centers and 244 clinics by 1996[12]. Nonetheless, the geographical access to DOT was limited as many patients live too far away from clinics (up to 50 km) to come for daily clinic DOT and led to inadequate tracing of treatment interrupters. Still, there was hardly any provision of community-based DOT.[12]

Furthermore, the high pill burden (i.e. 9-12 tablets per day) of first line single-drug DOT formulations compromised the adherence and the effectiveness of the medication, particularly among patients on co-medication for TB and HIV. Besides, sputum-smear examination services were insufficient at hospitals (i.e. long distances between the 30 laboratories and hospitals, irregular specimen collection and smear result time turn-around time beyond 48 hours) and unavailable in health centers and clinics. This negatively impacted on the utility of sputum-smear for diagnosis and treatment follow-up. Consequently, in 2004 Namibia reported the emergence of drug resistant TB (DR-TB), the lowest TSR and highest CNR for tuberculosis.[12]

The community-based DOTS (CB-DOTS) strategy, designed to mitigate the persistently high CNR and low TSR despite a country-wide implementation of facility-based DOTS between 1995-2004, and which was effectively implemented in Namibia in March 2005 under the first and second medium-term plans (MTP-I, 2004-2009; MTP-II, 2010-2015) for Tuberculosis and Leprosy constitutes 'the intervention' in the interrupted time series analysis. The strategic goal of CB-DOTS was to improve TB diagnosis, cure and treatment completion through universal access (i.e. geographic and patient level) to high quality community-based tuberculosis care.

In particular, the CB-DOTS aimed to increase TSR for all patient categories from 65% to 85% by 2009 and to 90% by 2015. To achieve these goals, CB-DOTS implementation framework designated the National Tuberculosis and Leprosy Programme (NTLP) and health districts (34) as the coordination and implementing units respectively, to work in partnership with up to14 community-based organisations (CBOs) implementing TB or HIV care. The budget for implementing CB-DOTS was funded by the Government of Republic of Namibia (51%), Global fund (19%) and USAID (3%), among others through sub-grants to the CBOs.

This framework also paved the way for the introduction of Fixed-Dose Combination (FDC) drugs for first line tuberculosis treatment, CB-DOT training manual and national course, adoption of the WHO guidelines for TB treatment for supporters and universal access to high-quality low-cost DOT regimens, revision of TB guidelines to improve case

management and community-based DOT cards to track treatment outcomes were introduced[10,12]. By 2015, CB-DOTS coverage had scaled-up one pilot region (Omaheke in 2004) to 12 regions and 27 districts during MTP-I and to all 14 regions and 34 health districts during MTP-II, and a total of 529 community health workers (i.e. CHW: TB cases ~ 1:25 or 529/13147) were deployed. A team of community-based persons comprising of CHW (i.e. community-DOT supervisors and facility and DOT nurses), DOT field promoters, and community-DOT supporters implement the CB-DOTS programme at each health district unit.

The CBOs assist the district unit in early identification of TB cases and the provision of DOT in the community. The DOT-supporters (i.e. family/relatives, workplace peers, CHW) directly observe the administration of the TB-medication at community DOT points, households and workplaces. For instance, in 2015 in the Omaheke region 954 DOT supporters, 858 supervisors and 1189 DOT providers were deployed. In addition, the access to quality of CB-DOTS services was expanded scaled-up during MTP-II (2010-2015), that is to all 14 regions and 34/34 health districts, all 13 regional prisons, collaborative integration in all CBOs and sites implementing community-based HIV care, public-private workplace partnerships and mobile CB-DOT clinics.

Also, the quality of CB-DOTS was enhanced, through scale up of quality assured bacteriology laboratories from 30 (1 lab per 67,000 people) in 2004 to 36 out of the 80 planned labs in 2015 to increase case detection, a CB-DOTS training manual and WHO

guideline for TB treatment supporters to standardize treatment with supervision and patient support, a system for effective supply and management of TB drugs as well as a monitoring and evaluation system to for effective measurement.

3.3.2 Data collection

Quantitative population level data on annual TB rates of treatment success, cure (i.e. the proportion of cases with pulmonary (PTB), that is TB with lung parenchyma involvement, with bacteriologically confirmed TB at the start of treatment whose sputum was smear- or culture-negative in the last month of treatment), treatment completion (i.e. the proportion of TB cases in a given year that successfully completed TB treatment without bacteriological evidence of success), and case notification for all cases of TB registered during the period 1995 to 2015 were extracted from the annual reports of the National Tuberculosis and Leprosy Programme (NTLP) of the Ministry of Health and Social Services (MOHSS) of Namibia.[11]

In Namibia treatment success for extra-pulmonary TB (EPTB, i.e. TB disease at sites other than the lung parenchyma) is reported as the proportion of cases with/without aspirate bacteriological or cytology/histology results who are clinically well after completion of 6-8 months of treatment.[11] The National Institute of Pathology, an accredited laboratory performs all the bacteriological testing for TB cases in all DOTS sites in Namibia. Consequently, a case of cure is confirmed by a medical officer based on TB guidelines, which are implemented at all DOT sites with supported training. These annual rates are

based on aggregates of quarterly reports collated by quality assurance teams from district and regional TB case registers.

The annual rates were validated against the WHO Analytical Country Summaries for TB, as well as the data reported by the World Bank, United States Agency of International Development (USAID) and Global Fund.[1] Twenty validated annual TSR, CNR from 1995/1996 – 2014/2015 for cases with PTB, EPTB, drug susceptible TB (DST) and drug resistant TB (DR-TB) were included in the study. Annual rates reported before 1995 were excluded since there was no systematic reporting on TB outcomes before the establishment of the NTLP programme in 1991.[10,11]

During the study period, the case definitions for cure and treatment completion did not change and the DOTS services were free of cost and treatment support as the only incentive during CB-DOTS.

3.3.3 Statistical analysis

An interrupted time series (ITS) analysis was conducted to establish the underlying trend in tuberculosis treatment success, cure and completion rates for all TB cases during the period 1996-2015. The effect of implementation of a country-wide community-based DOTS in Namibia in 2005, i.e. the intervention, on the treatment success, cure, and completion rates was also assessed by ITS.[15] The interrupted time series analysis is explained in more detail below.

3.3.4 Segmented regression model for treatment success, cure and completion rate

An interrupted time series analysis was carried out to assess the effectiveness of CB-DOTS strategy on TSR, CNR, cure and treatment completion rates for all cases. Interrupted time series analysis is a valuable study design for evaluating the effectiveness of population-level health interventions that have been implemented at a clearly defined point in time.[15]

In this design, pre-intervention regression level and trend of the outcome measure act as controls for the post-intervention segment.[15] The intervention was the expansion of FB-DOTS to CB-DOTS in Namibia. The effective time for implementation of the CB-DOTS strategy was set at 2005, one year after the implementation of MTP-I. This considered a one-year phase-in period since a full cycle of completion of DOTS lasts between 6-8 months for a patient with drug sensitive TB and reporting of the treatment success rate in the subsequent year.

The outcome variables were the TSR, defined as the percentage of patients who were cured and/or completed DOT in a particular year under review, the treatment completion rate and the annual CNR.[11] The impact of CB-DOTS on TSR, cure and completion rates, and covariates such as HIV prevalence, CB-DOTS and ART coverage was determined by the change in level (β_2) and trend (β_3) in the treatment outcome in the pre and post-intervention period after 2005 by a segmented regression model using RStudio v3.3.2 as detailed below.

The following segmented regression model was used to determine the level and trend changes in tuberculosis treatment success, cure and completion:

$$Y_t = \beta_0 + \beta_1 * T + \beta_2 * X_t + \beta_3 * T * X_t + \beta_w * T * X_t + e_t$$

Y_t is the outcome, i.e. treatment success rate or case notification rate at time t, T is the time (in years) that elapsed since the start of the study, X_t is a dummy variable indicating the pre-intervention period (coded 0) or the post-intervention period (coded 1); β_0 estimates the baseline outcome at T=0; β_1 is an estimate of the pre-intervention outcome trend (i.e. the change in outcome with time); β_2 is an estimate of the change in outcome immediately after the intervention, i.e. compared to the outcome at the end of the pre-intervention period; β_3 estimates the change in the post-intervention outcome trend compared to the pre-intervention outcome trend; β_w estimates the impact of the wild point in 2004 (i.e. the unexpectedly low TSR and cure rate, or unexpectedly high completion rate, in 2004 relative to preceding years) which was excluded from the final model; e_t represents the random variability not explained by the model.

The TSR in 2004 was modeled as a wild point (i.e. there was an abrupt drop in TSR in that year relative to the preceding years (1996-2004). This unexpected drop in TSR may have been due to the transition from the FB-DOTS to the CB-DOTS policy, the high incidence of TB and HIV in that year as well as programmatic challenges for switching to fixed-dose combination anti-tuberculosis medicines. The impact of population time varying covariates such as TB incidence, HIV prevalence and ART (antiretroviral) coverage on TSR and/or CNR were modeled individually as $\beta_i * T * X_i$ alongside the Y_t

parameters. Adjustment for serial autocorrelation was carried out by using the Durbin-Watson statistic and an autocorrelation parameter was included in the segmented regression model.

3.3.5 Prediction of the maximum possible treatment success rate under CB-DOTS

To estimate the maximum treatment success rate that could theoretically be expected based on the observed post-intervention treatment success rates, nonlinear regression analysis was carried out using the following model predicting the maximum outcome as a function of time after the intervention:

$$TSR = A + \frac{TSR_{max} \cdot T}{T_{50} + T}$$

in which A is the TSR level at the intervention estimated by the segmented regression model, TSR_{max} is the maximum treatment effect rate, T_{50} is the time at which the outcome is 50% of TSR_{max}, and T is the time (in years) after the intervention. For all statistical tests, a p-value of ≤0.05 was considered to be significant. An exponential analysis predictive. Model was used after observing that at the end of MTP-II, TSR points had stagnated at less than 90%.

3.3.6 Ethics

Data reported in public documents by the health authorities of Namibia were used as the primary source to assess the effectiveness of an intervention at the population level. Ethical approval for the study was obtained from the human ethics committees of the

MOHSS (MoHSS17/3/3/November 2015) and the University of Namibia (SOM/114/2016).

3.4 Results

The annual number of case notifications by TB category and the TSR, CNR, and population covariates from 1996 to 2015 are shown in Figures 1 and 2, respectively. The mean (± SD) treatment success rate during the pre-intervention period was 58.9 ± 6.9% but varied considerably from year to year (range: 46% to 66%) (Figure 2). After implementation of CB-DOTS in 2005, a slow but steady increase in the annual TSR was observed: during MTP-I it was on average 76.4 ± 4.8 % and during MTP-II 85.3 % ± 1.4% (p<0.001). During the post CB-DOTS implementation period, the mean annual TSR was significantly higher than during the pre-intervention period. After the implementation of the CB-DOTS strategy, the CNR, which had been around 800/100,000 just before the intervention, started to gradually decline to 436/100,000 in 2015. A significant inverse correlation (r = -0.65, p=0.001) was found between the CNR and the TSR.

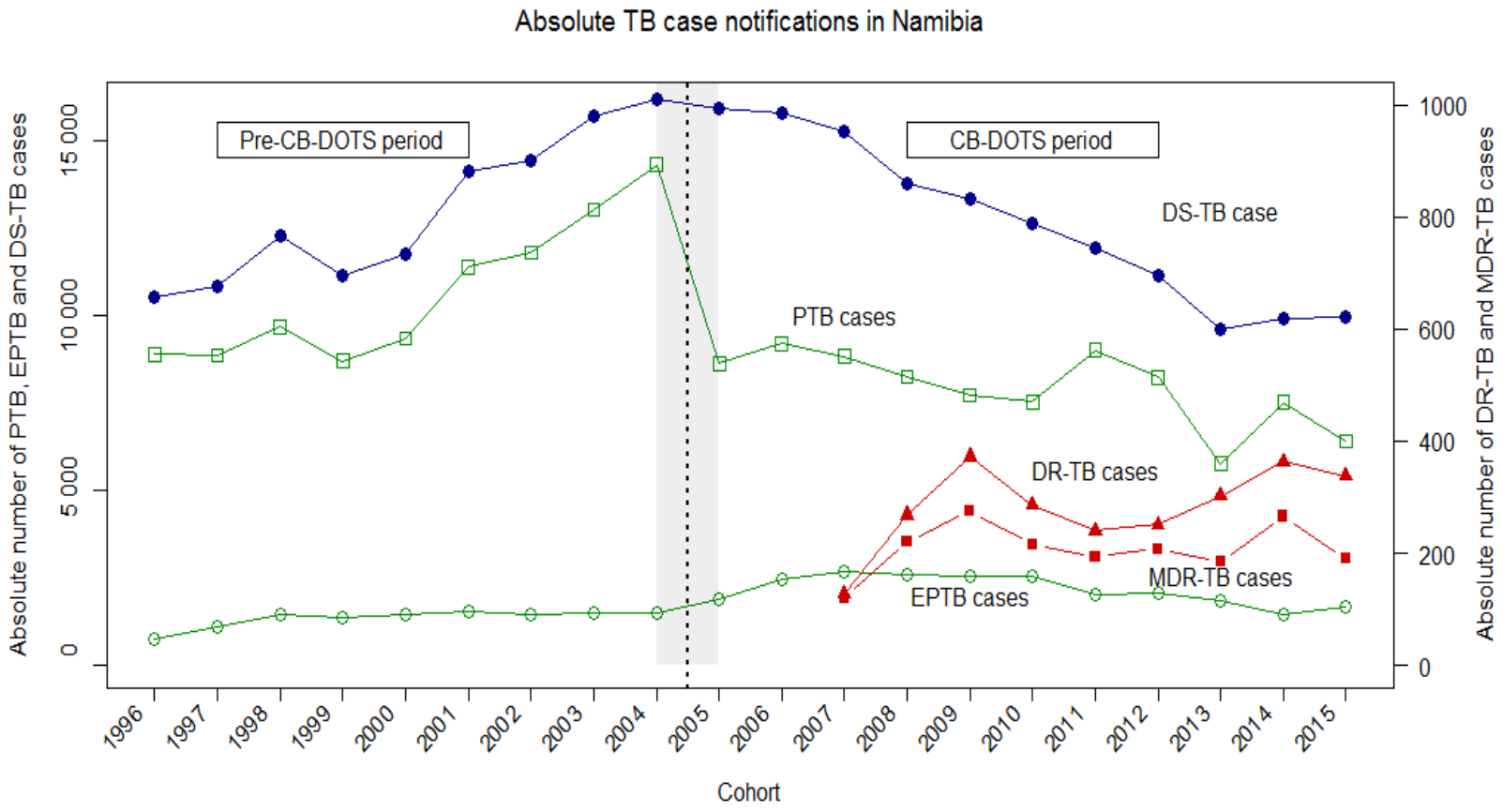

Figure 1: Annual number of cases of drug susceptible tuberculosis (DST-TB, ●), drug resistant tuberculosis (MDR-TB, ▲), multi-drug resistant tuberculosis (MDR-TB, ■), pulmonary tuberculosis (PTB, □) and extra pulmonary tuberculosis (EPTB, ○), during the period 1996-2015.

The results of the final, i.e. after correction for autocorrelation, segmented regression model of the TSR, CNR, cure and treatment completion rates for all cases with drug susceptible TB are summarized in Table 1 and Figure 3a. The model estimated TSR at the beginning of the pre-intervention period (β_0) at 58.0% and the CNR at 596.7/100,000. During the pre-intervention period the annual change in TSR, CNR and cure rate (β_1) was positive, indicating an increase in trend, which was only statistically significant for cure rate (p=0.0172). The treatment completion rate during the pre-intervention period showed a slight, non-significant decrease.

On the contrary, during the pre-intervention period, the CNR increased significantly by 23.9/100,000 cases/year. After the intervention, the treatment success and treatment completion rates (β_2) increased abruptly and significantly ($p<0.001$) by 12.9% and 24.3%, respectively, from the estimated level at the end of the pre-intervention period, e.g. from 60.9% to 68.0% for TSR (Figure 3a). In contrast, the cure rate abruptly dropped after the CB-DOTS intervention by 18.6% ($p<0.001$). The immediate post-intervention change in the CNR was not statistically significant (Table 1).

After the intervention, the trend in the annual TSR, cure and completion rates (β_3) increased, but this was only statistically significant for TSR and cure rate. The post-intervention trend of CNR significantly decreased by 60.6/100,000 notifications per year. The wild point (i.e. unexpected and unexplained drop in TSR) at 2004 was associated with a significant drop in treatment success and cure rates ($p<0.001$), but not treatment completion rate (Figure 3a).

After the intervention there was a significant ($p<0.005$) immediate increase in level and/or annual rates for treatment outcomes for pulmonary versus extra pulmonary (Figure 3c-d, Table 1) and DST-TB versus DR-TB (Figure 3a-b, Table 1) and the different classes of PTB categories, i.e. new smear positive, retreatment and smear negative cases (Table 1, Figure 4a-d).

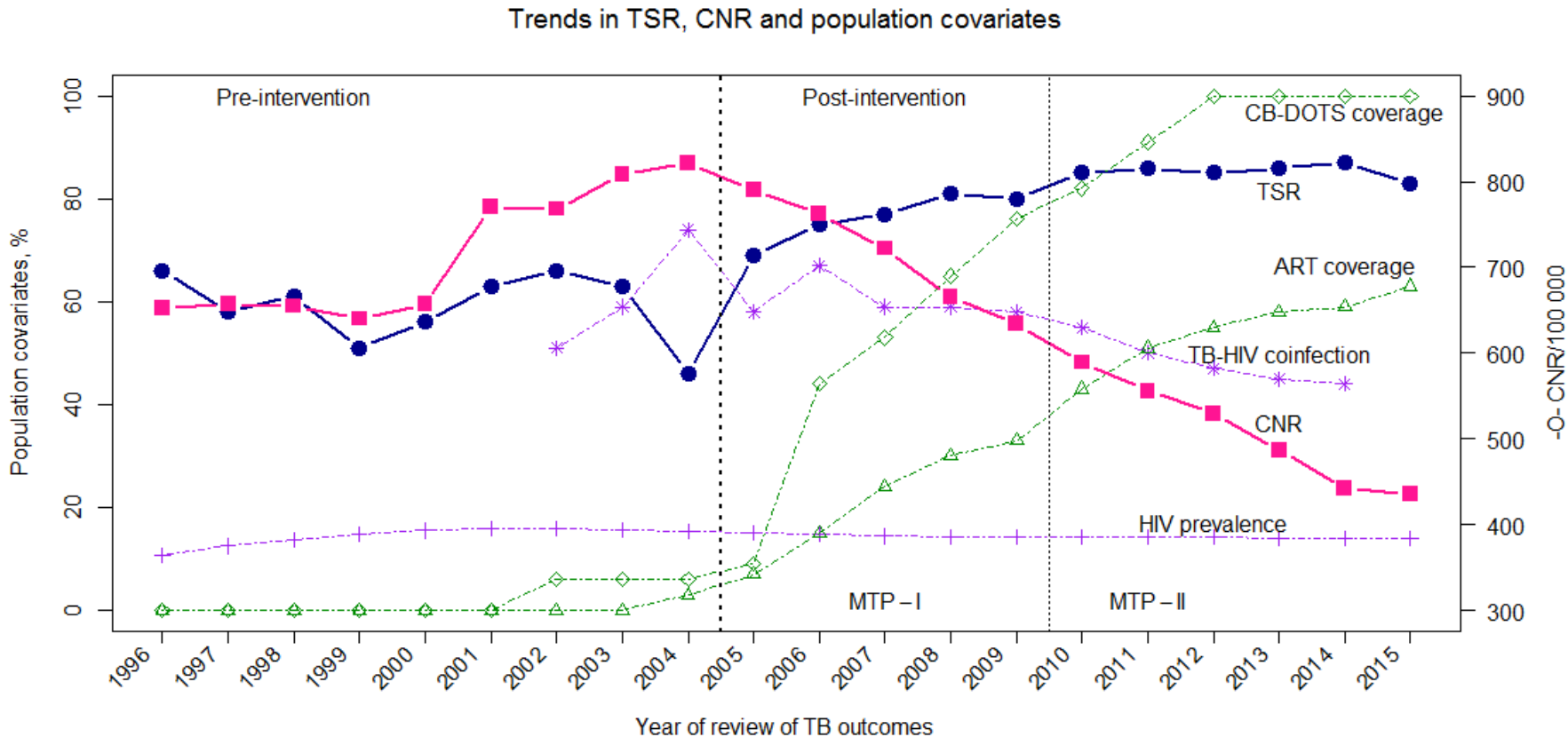

Figure 2 Annual case notification rates (CNR, ■), CB-DOTS coverage (◇), adult HIV prevalence (+), ART coverage (△) and prevalence of HIV among TB patients (✳), and treatment success rate (TSR, ●) during the period 1996-2015. *Data source: Annual MoHSS National TB and Leprosy reports, Global TB reports and WHO TB database.*[1,2]

Table 2 shows the impact of population covariates on TSR, cure and completion rates. During the post-intervention period, the increased national CB-DOTS and/or ART coverage significantly increased the TSR for all TB cases (Table 2). The impact of time varying covariates on treatment, cure and treatment completion rates for all TB cases was more significant with increased CB-DOTS and ART coverage (Table 2). HIV prevalence significantly reduced TSR, cure and completion rates among cases with DST-TB by 4.4%, 3.0% and 2.9%, respectively. The declining CNR had virtually no impact on treatment outcomes, but marginally increased the treatment completion rates among PTB and DST-TB.

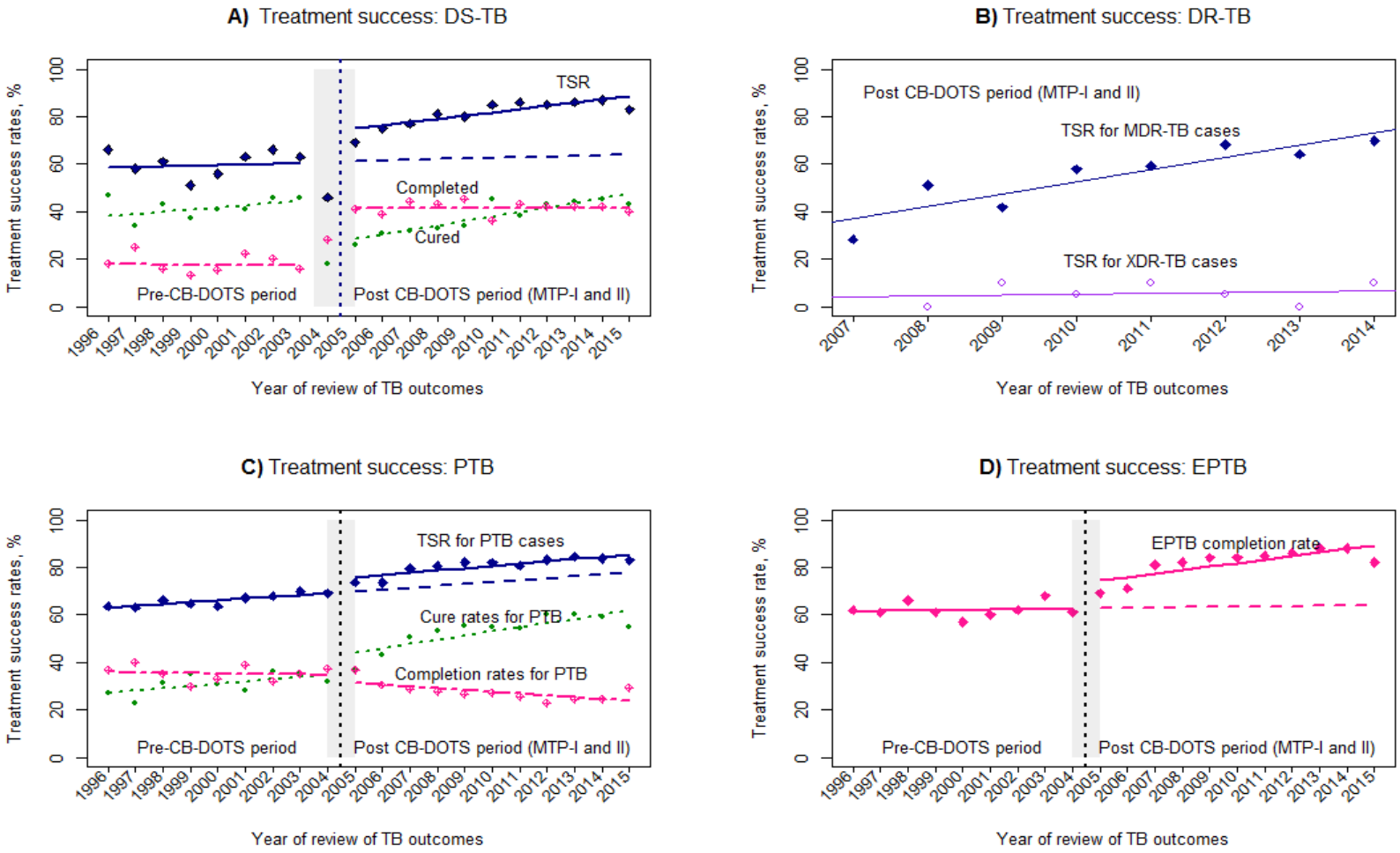

Figure 3: Interrupted time series analysis of the annual treatment success rate (■), cure rate (●), and treatment completion rate (◈). The predicted pre- and post-intervention trends, based on the final segmented regression model, are shown by the lines.

Table 2: Estimated coefficients for the interrupted time series analysis of treatment success rate (TSR), cure rate, treatment completion and case notification rate (CNR).

	PRE-INTERVENTION LEVEL (β_0)		PRE-INTERVENTION TREND (β_1)		POST INTERVENTION LEVEL CHANGE (β_2)		POST-INTERVENTION TREND CHANGE (β_3)	
	Estimate (95%CI)	p-value	Estimate (95%CI)	p-value	Estimate (95%CI)	p-value	Estimate (95%CI)	p-value
PULMONARY TUBERCULOSIS (PTB)								
Pulmonary tuberculosis (all cases)								
Treatment success rate (%)	62.1 (59.4,64.9)	<0.001	0.9 (0.3,1.3)	0.003	5.6 (2.2,8.9)	0.003	0.2 (-0.4,0.8)	NS
Cure rate (%)	26.1 (19.8,32.3)	<0.001	0.95 (-0.2, 2.1)	NS	7.7 (-0.01, 15.32)	NS	0.8 (-0.6,2.2)	NS
Completion rate (%)	36.0 (31.1,41.0)	<0.001	-0.2 (-1.04,0.72)	NS	-2.4 (-8.5,3.7)	NS	-0.6 (-1.7, 0.5)	NS
New smear positive PTB								
Treatment success rate (%)	64.8 (61.8,67.8)	<0.001	0.5 (-0.004,1.070)	NS	7.1 (3.4,10.8	0.002	0.6 (-0.1, 1.2)	NS
Cure rate (%)	44.2 (37.1. 51.5)	<0.001	0.9 (-0.4,2.1)	NS	12.1 (3.2,21)	0.017	0.3 (-1.3,1.9)	NS
Completion rate (%)	20.5 (15.6,25.5)	<0.001	-0.3 (-1.2,0.6)	NS	-5.4 (-11.4,0.7)	NS	0.2 (-0.9,1.3)	NS
Retreatment (smear positive) PTB								
Treatment success rate (%)	63.3 (58.8,67.8)	<0.001	-0.5 (-2.6,1.5)	NS	2.5 (-2.9,8.0)	NS	2.2 (1.2,3.1)	<0.001
Cure rate (%)	41.5 (30.0,53.0)	<0.001	-0.04 (-1.9,1.8)	NS	0.1 (-13.9,14.3)	NS	3.4 (0.9,5.9)	0.018
Completion rate (%)	22.0 (11.5,32.4)	<0.001	1.6 (0.9,2.3)	NS	2.4 (-10.5,15.2)	NS	-0.9 (-3.2,1.4)	NS
Smear negative Patients PTB								
Completion rate (%)	57.7 (53.7,61.7)	<0.001	1.6 (0.9,2.3)	<0.001	6.1 (1.2,11.0)	0.028	-1.1 (-2.0,-2)	0.024
EXTRAPULMONARY TUBERCULOSIS (EPTB)								
Completion rate (%)	61.3 (55.5,66.8)	<0.001	0.1 (-0.8,1.1)	NS	10.4 (3.7,17.1)	0.008	1.3 (0.1,2.6)	0.044
DRUG SENSITIVE TUBERCULOSIS (DST-TB) $^{\phi}$								
Treatment success rate (%)	58 (53.6,62.9)	<0.001	0.3 (-0.7,1.2)	NS	12.9 (6.8,18.9)	<0.001	1.1 (0.1,2.1)	0.046
Cure rate (%)	37.2 (34.1,40.4)	<0.001	0.9 (0.2,1.5)	0.017	-18.6(-22.5,-14.7)	<0.001	1.0 (0.2,1.7)	0.020
Completion rate (%)	17.8 (15.5,20.1)	<0.001	-0.06 (-0.5,0.4)	NS	24.3 (21.6,27)	<0.001	0.05 (-0.5,0.6)	NS
MDR TUBERCULOSIS (MDR-TB)								
Treatment success rates (%)			N/A		-21.3 (-52.9,10.4)	NS	4.9 (3.0,6.9)	<0.001
CASE NOTIFICATION RATE (CNR/100,000)	596.7 (553.1,640.3)	<0.001	23.9 (16.4,31.5)	<0.001	10.1 (-39.1,59.2)	NS	-60.6 (-70.6, -50.7)	<0.001

$^{\phi}\beta_w$ (impact of the wild point in 2004, i.e. unexplained low treatment success rate): TSR -13.6 (-21, -6.4), *p*=0.002; Cure rate 27.4 (-36, -20.1), p<0.001 and Treatment c ompletion 12.0 (6.5,17.5), p<0.001. *NS: not significant; CI: confidence interval. Durbin Watson statistic for TSR data = 2.9 (lag=3, p= 0.034); Durbin Watson statistic for CNR data = 1.3 (lag=1, p=0.012). N/A: not applicable; There were no data on MDR in the pre-intervention period to make comparisons.*

Table 2:Impact of population time varying co-variates on treatment success, cure, treatment completion rates.

Population covariate	**Case notification rate (CNR /100,000)**		**National adult HIV prevalence (%)**		**CB-DOTS coverage (% districts)**		**National ART coverage (% districts)**	
	Estimate (95%CI)	p-value	Estimate (95%CI)	p-value	Estimate (95%CI)	p-value	Estimate (95%CI)	p-value
PULMONARY TUBERCULOSIS								
Pulmonary tuberculosis (all cases)								
Treatment success (%)	0.1 (-0.3,0.5)	NS	-0.7 (-2.1,0.7)	NS	0.1 (0.02,0.2)	0.015	0.3 (-0.02,0.6)	NS
Cure rate (%)	-0.7 (-1.5, 0.1)	NS	0.6 (-2.7,3.9)	NS	0.3 (0.2,0.5)	0.001	0.7 (0.05,1.39)	0.037
Completion rate (%)	0.8 (0.3,1.4)	0.007	-1.3 (-3.8,1.3)	NS	-0.2 (-0.4,-0.08)	0.006	-0.52 (-1.1,0.03)	NS
New smear positive PTB								
Treatment success (%)	0.02 (-0.4,0.5)	NS	-0.7 (-2.4,1.0)	NS	0.12 (0.001,0.23)	0.047	0.24 (-0.15,0.63)	NS
Cure rate (%)	-0.4 (-1.5,0,7)	NS	-0.8 (-4.9,3.2)	NS	0.3 (-0.08,0.54)	NS	0.37 (-0.59,1.3)	NS
Completion rate (%)	0.4 (-0.3,1.2)	NS	0.1 (-2.6,3.0)	NS	-0.2 (-0.36,0.02)	NS	-0.30 (-0.94,0.35)	NS
Retreatment (Smear positive) PTB								
Treatment success (%)	0.15 (-0.5,0.8)	NS	0.8 (-1.7,3.3)	NS	0.11 (-0.07,0.29)	0.204	0.17 (-0.42,0.76)	NS
Cure rate (%)	-0.95 (-2.6,0.7)	NS	2.5 (-4.0,8.9)	NS	0.7 (0.45,1.02)	<0.001	1.52 (0.21,2.83)	0.026
Completion rate (%)	1.1 (-0.3,2.6)	NS	-1.8 (-7.7,4.1)	NS	-0.6 (-0.9, -0.4)	<0.001	-1.25 (-2.49, -0.01)	0.048
Smear negative patients PTB								
Completion rate (%)	0.25 (-0.4,0.8)	NS	-1.8 (-3.4,0.3)	NS	0.2 (0.06,0.33)	0.007	0.7 (0.3,1.1)	0.001
EXTRA-PULMONARY TUBERCULOSIS								
Completion rate (%)	0.04 (-0.8,0.9)	NS	-1.5 (-4.5,1.5)	NS	0.3 (0.1,0.5)	0.004	0.72 (0.09,1.35)	0.026
DRUG SENSITIVE TUBERCULOSIS (DS-TB)								
Treatment success (%)	0.1 (-0.001,0.1)	NS	-4.4 (-7.7, -1.1)	0.021	0.5 (0.1,0.9)	0.032	0.8 (0.3,1.2)	0.004
Cure rate (%)	0.04 (-0.02, 0.09)	NS	-3.0 (-4.8,1.2)	0.005	0.5 (0.2,0.7)	0.003	0.5 (0.2,0.8)	0.003
Completion rate (%)	0.1 (0.04,0.14)	0.001	-2.9 (-4.4, -1.4)	0.002	0.1 (-0.2,0.4)	NS	0.05 (-0.3, 0.4)	NS

NS: not significant; CI: confidence interval. Estimate = is the impact, i.e. the percentage change, that a covariate had on the treatment outcome after the implementation of CB-DOTS in 2015.

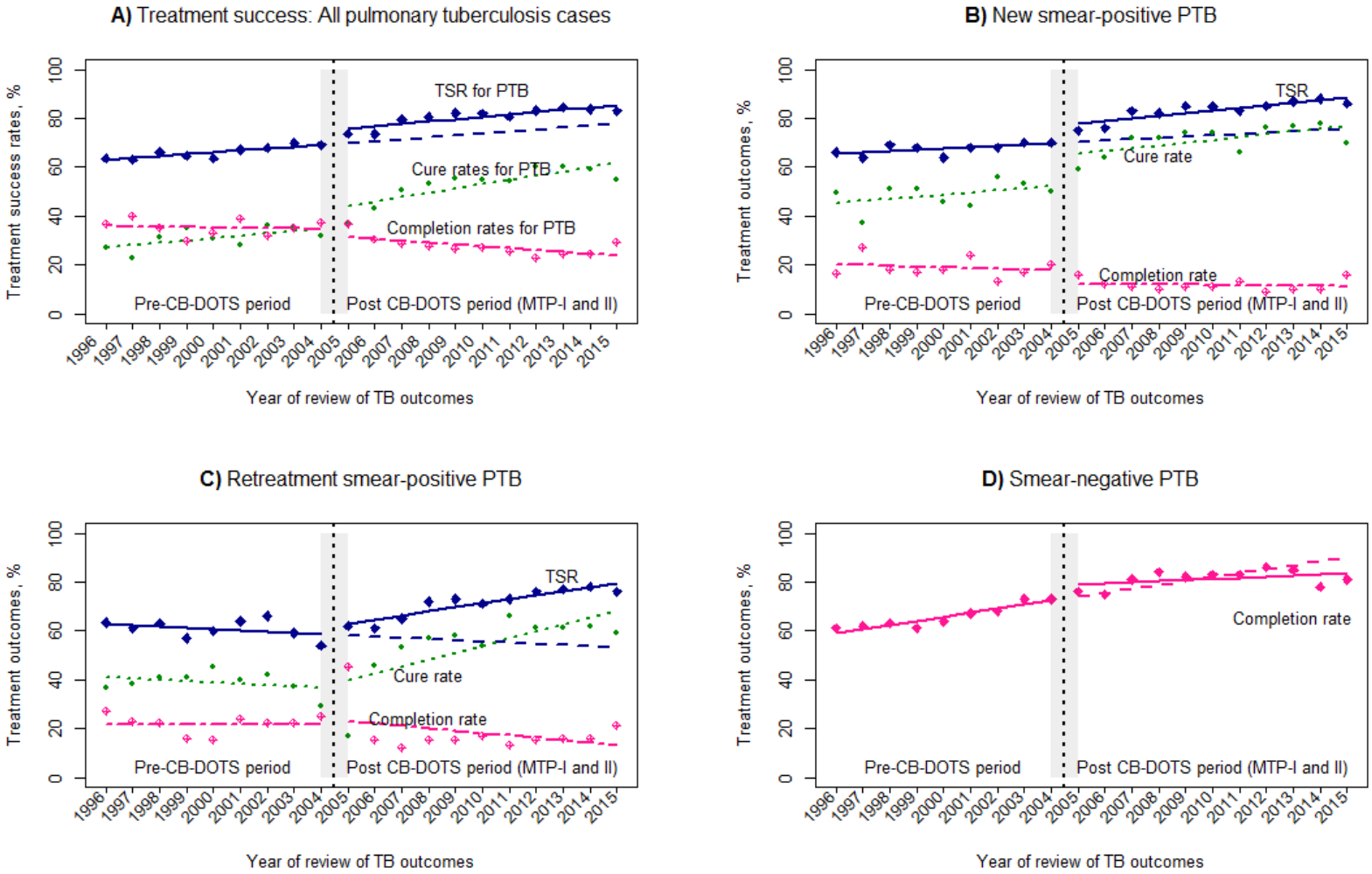

Figure 4: Interrupted time series analysis of the annual treatment success rates (◆), cure rates (●), and treatment completion rates (◈) by PTB categories, i.e. new smear positive cases, retreatment cases and negative smear patients. The predicted pre- and post-intervention trends, based on the final segmented regression model, are shown by the lines.

After the intervention the annual treatment success rate seemed to increase non-linearly and tended towards a maximum which was estimated at 92.4% (95% CI: 87.7% - 97.1% r^2: 0.961) with current interventions (Figure 5). However, the approach to this estimated maximum treatment rate is very slow with a 90% treatment success rate estimated to be reached in 2025.

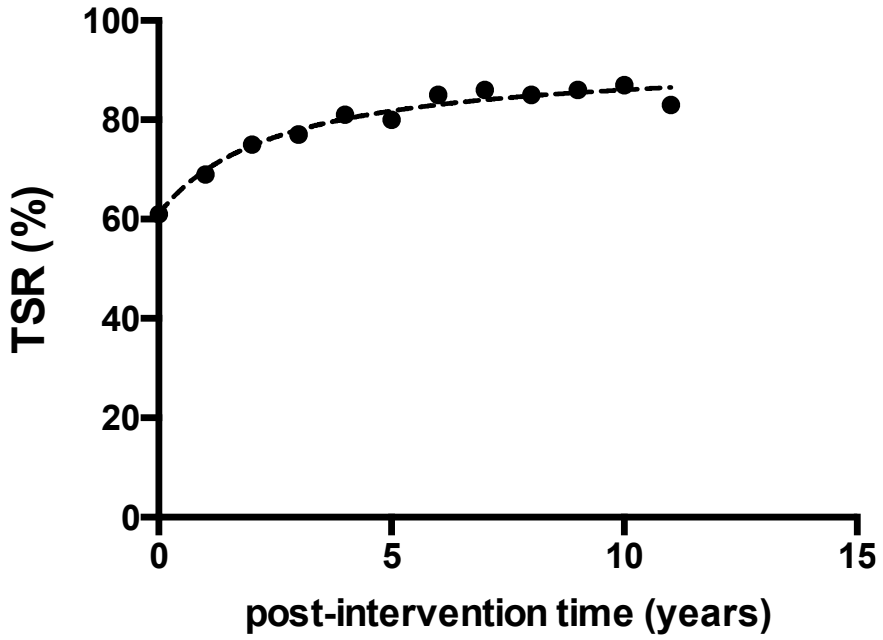

Figure 5: The maximum effect model fitted the post-intervention treatment success rates (TSR) very well (r^2=0.961) with a predicted maximum TSR of 92.4%.

3.5 Discussion

Directly observed therapy, as recommended by the World Health Organization, is used in many countries to deliver TB treatment.[3,4,6] The effectiveness of community-based versus facility-based (or clinic) DOTS has not been systematically assessed to date. Wright et al.

performed a review and meta-analysis of 8 studies, carried out before 2015, comparing treatment outcomes of CB-DOTS versus FB-DOTS.[9] They concluded that CB-DOTS had a higher treatment success rate with a pooled odds ratio of 1.54 (95% confidence interval: 1.01 – 2.36; $p = 0.046$).

FB-DOTS was introduced in Namibia in 1991 and was universally accessible at all public health facilities in 1996, and was later expanded in 2005, to CB-DOTS. Before implementation of CB-DOTS, the annual TSR in Namibia was around 60% but showed high variability from year to year (range: 46% to 66%). During the same period, the CNR slowly increased from 652/100,000 to 822/100,000 population, which is among the highest in the world.[2] The first year after the introduction of CB-DOTS, the TSR and completion rate, but not cure rate, showed a significant increase compared to the pre-intervention success rate level.

A review of MTP-I in 2010 attributed the sub-optimal cure rates to persistence of inadequate access to quality TB diagnostic services and direct observation of TB treatment due to the geographic vastness of the country (second lowest population density in the world) impeding not only patients level CB-DOTS coverage but also the quality and turn-around time of TB direct microscopy results in remote areas and among highly mobile populations.[12] The introduction of the electronic TB database in 2005 as a component of CB-DOTS may have increased the reporting of treatment outcomes which may explain the abrupt rise in TSR between 2004 and 2005. During the post-intervention period,

treatment success rates continuously increased by 1.1%/year from 69% in 2005 to 88% at the end of 2015.

Time varying covariates such as CB-DOTS coverage, HIV prevalence and ART coverage only marginally affected the TB treatment outcome rates for all TB cases. However, the effect of other potentially important covariates such as quality and availability of anti-TB medicines and drug-resistance patterns could not be tested due to the lack of proper data. Not surprisingly, the improvement of TSR after the implementation of CB-DOTS alongside other MTP interventions was accompanied by a gradual decrease in the CNR from 822/100,000 at the end of the pre-intervention period to 436/100,000 ten years later. This decrease in the annual CNR was inversely correlated to the treatment success rate (r^2 = 0.46; p = 0.0011), but other factors such as improved programmatic detection of new TB cases and preventative control measures through community-based TB care as well as the improved access to quality DOTS services nationwide.

However, the improvement of the treatment outcome rates following the expansion of FB-DOTS to CB-DOTS falls short of the targets set by the NLTP/MOHSS under MTPI& II. The targets for treatment success rate under MTP-I and MTP-II were 85% and 90%, respectively. Although the target of the MTP-I programme was met, at the end of 2015 the treatment rate had seemingly stagnated around approximately 85%, which falls short of the MTP-II target of 95%. Even if the success rate would still have continued to increase during that final year, at the projected 1.1%/year, the 90% target would still not have been

reached. Moreover, the success rate data are clearly leveling off towards the end of the MTP-II programme. Based on the data, it would still take several decades to reach the predicted theoretical maximum success rate of approximately 92%.

It is clear that the community-based DOTS strategy alone will not be able to "end TB". Other factors which cannot be controlled by community-based DOTS must be explaining why the treatment success rates are stagnating around 90%. Similar studies in other countries have concluded that stagnation of treatment success rates below the 95% target may favour drug resistant TB and recommend modifications to the DOTS strategy.[16-19] In low to middle income countries like Namibia, the effectiveness of DOTS is compromised by false negative smear results, the limited monitoring of bacteriological end points, and the growing burden of drug-resistant TB.[20-24]

Consequently, community-based DOTS should be improved by implementing additional strategies to identify patients at risk of poor treatment outcomes to reach WHO's goal to "end TB" by 2035. These additional community-based measures should focus on ways to improve treatment monitoring and outcomes in TB patients with co-morbidities such as HIV infection and diabetes, in childhood TB, in malnourished patients and other or mobile patient groups with an increased risk of treatment failure.[17, 21, 25-30] In addition, the use of treatment completion as a surrogate measure of treatment success should be validated across all TB cases in the context of programmatic challenges. In addition, some communities/patients may require personalized rather than standardized DOTS approach

to optimise treatment outcomes. Nonetheless, the ITS model used had no data from a TB programme similar to Namibia to be used as a control.

However, the findings should be interpreted bearing the limitations of the ITS design that uses population level data/indicators and not raw data from the cases and may not account for any errors in data collection and aggregation as well as lack of data on time varying covariates such a number of HW trained, supply of medicines etc. None-the-less, the improvement in the quality of data reported is a strategic objective of the CB-DOTS programme in Namibia where quality is assured a facility, district, region and national levels.

In conclusion, the results of this study demonstrate that community-based DOTS is more effective than facility-based DOTS to increase the TB treatment success rate. In Namibia, the community-based DOTS strategy, however, was not, and will not be, able to reach the target of 95% success rate. Additional measures such as bacteriologic monitoring among patients at risk of therapeutic failure, is critical to "end TB" by 2035. We are currently exploiting the extensive electronic TB database of the NLTP/MOHSS in an attempt to identify significant predictors of poor TB treatment outcome in Namibia.

Acknowledgements

The authors wish to acknowledge the assistance rendered by the staff at the National Tuberculosis and Leprosy Programme, Ministry of Health and Social Services Namibia in accessing of the data from the TB registers.

The authors declare no conflict of interest. This study did not receive any specific grant from any funding agency in the public, commercial or non-profit sectors. Dr. Law received salary support through a Canada Research Chair and Michael Smith Foundation for Health Research Scholar Award.

Author contributions

DK played the leading role in conceptualizing, data collection, analysis and write up of the manuscript. ML supported the analysis with ITS modelling data collection. RN, RA, AT assisted in data collection and cleaning. RV, GG, TR and BG edited and appraised the paper during the various stages of publication. All authors permitted the submission of this paper to this journal.

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CHAPTER 4-6: MODELING PATIENT-LEVEL MODELING OF PREDICTORS OF TUBERCULOSIS TREATMENT OUTCOMES IN NAMIBIA

OVERVIEW

Chapter 4, 5 and 6 aimed to identify the patient-level predictors of three key tuberculosis treatment outcomes, i.e. treatment success rates (TSR), loss to follow-up and case-fatality rates using regression modelling. Thus patient level studies indicated in three chapters i.e. Chapter 4, 5 and 6 to represent the respective studies. Chapter 4 describes a statistical model for independent predictors of TB treatment success rate under the DOTS programme in Namibia. Chapter 5 describes a model for patient level predictors of loss to follow-up of TB cases under the DOTS programme in Namibia.

Chapter 6, describes two sub-studies using hospital-based data and a nationawide database modelled patient-level predictors of tuberculosis case-fatality under the DOTS programme in Namibia. The predictors in the three studies provides insights on programmatic, clinical and/or patient related gaps in the current DOTS programme that require strengthening.

CHAPTER 4: PATIENT LEVEL MODELING OF TREATMENT SUCCESS RATES IN NAMIBIA

Predictors of Tuberculosis treatment success rates under the DOTS programme in Namibia

Published in *Expert Review of Respiratory Medicine. 2018 Nov; 12(11):979.*

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4.1 Abstract

Setting: Optimal treatment success rates are critical to end tuberculosis in Namibia. Despite the scale-up of high-quality DOTS in Namibia, treatment success falls short of the global target of 90%.

Objective: The predictors of treatment success rates under DOTS in Namibia were assessed to provide future direction.

Methods: A nation-wide comparative analysis of predictors of treatment success was carried out. Tuberculosis cases in electronic tuberculosis register were retrospectively reviewed over a 10-year period, 2004-2016. The patient, programmatic, clinical and treatment predictors of treatment success were determined by multivariate logistic regression modeling using R software.

Results: A total of 104,603 TB cases were registered at 300 DOTS sites in 37 districts. The 10-year period treatment success rate was 80%, and varied by region (77.2%-89.2%). The patient's sex and age were not significant predictors of treatment success. The independent predictors for treatment success were: region of DOTS implementation (p=0.001); type of DOT supporter (p<0.001), sputum conversion at 2 months (p=0.013); cotrimoxazole prophylaxis OR= 0.4(95%CI: 0.2, 0.7, p=0.002); HIV co-infection OR=0.2(95%CI: 0.1, 0.5, p=0.001) and the DOT regimen (p<0.001).

Conclusions: Targeted programmatic, clinical and treatment interventions are required to enhance DOTS treatment success in Namibia.

KEY WORDS: TREATMENT SUCCESS RATES, PREDICTORS, TUBERCULOSIS

4.2 Introduction

Tuberculosis (TB), is the leading cause of death worldwide from an infectious disease. [1–3] In 2015 alone, the WHO estimated that TB killed about 1.8 million people globally; 95% of these deaths occurred in developing countries such as Namibia. [4] However, TB can be cured [5–8], and the WHO and the UN Sustainable Development Goals (SDGs) for 2030, calls for a 90% reduction in deaths and an 80% reduction in incidence rates by 2030 versus 2015.[9,10] The SDGs use treatment success rates (TSR, i.e. proportion of patients that are cure or complete treatment) and the case detection rate (CDR, i.e the percentage of TB cases notified against the estimated number cases for that year) as yardsticks for the control of TB.

Global initiatives have expanded DOTS (i.e Directly Observed Therapy Short-course strategy) services and markedly improved CDR and TSR in Lower and Middle Income Countries (LMIC) including Namibia.[11–15] Nevertheless, although TB incidence rates have been decreasing across countries, Namibia remains a high TB burdened country [4]. In addition, despite the 100% scale-up of high quality and community-based Directly Observed Treatment (DOT), Namibia still falls short of the national and global targets for TSR of 95%.[13,16]

Recent analysis suggests that TSR in Namibia have reached a maximum of less than 95% global bench mark, and improvements have been marginal in the past decade. [11,15,17] The TSR are even lower among the retreatment and smear negative cases. [18] [13] The sub-optimal treatment success rates are thus a major concern towards eliminating TB in Namibia. Moreover, stagnation in TSR in Namibia in the past decade (2004-2015), coincides with

the rising burden of drug resistant tuberculosis (DR-TB).[19] Evidence in Namibia and other LMICs suggests that current DOTS strategies are not comprehensive enough to "End TB" by 2035. [2,11,20–24]

However, there are conflicting reports on the impact of the various risk-factors in different populations – particularly pharmacokinetic variability , socio-demographic and baseline clinical characteristics. [25–27] To date, the magnitude and impact of these risk factors on treatment outcomes has not been systematically evaluated in Namibian and other LMIC where the burden of TB remains high.[9]

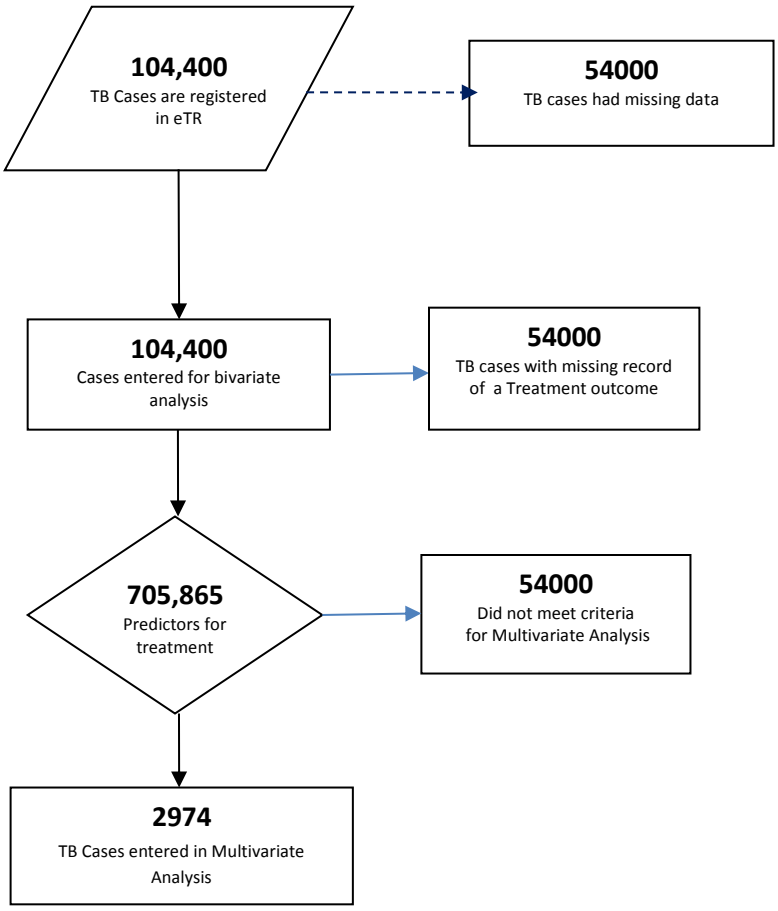

Figure 1: Flow chart for inclusion criteria of TB cases

4.3 Methods

4.3.1 Study design and population

A retrospective comparative analysis was carried out to determine the predictors of DOT treatment success and cure/treatment completion rates among cohorts of TB cases initiated on first line regimens. The study subjects were all new and retreatment cases registered in the national electronic TB register (ETR) of Namibia between the third quarter of 2004/Q3 and first quarter of 2016/Q1. The particular period, 2004-2015 was selected because

before 2004 there was no consistent programme to ensure collection of quality TB data. In 2004, under the MTP-I the electronic database and a system to assure quality of TB data was implemented.

In Namibia, high quality DOTS services that include directly observed treatment (DOT) are accessible at all public health facilities (i.e. facility based, FB-DOTS) or in all communities (i.e. community based, CB-DOTS) in all the14 geographical regions of Namibia. The FB-DOTS services can be accessed across all levels of care: primary health care (health centers and clinics) as well as at district, regional and referral hospitals. On the other hand, CB-DOTS services are provided by community-based DOTS workers that include DOT supervisor, DOT Nurse and DOT supporters who directly observe TB treatment and include: health facility nurse, work-place peers, and community-based workers, guardians (family/neighbor/relative) and any other as preferred by the patient. Nevertheless, DOT regimens are initiated at a health facility and supported either by community and/or facility-based providers.

Data on patient and clinical covariates and treatment outcomes for each patient is recorded on TB treatment cards. The data on treatment outcomes is subsequently aggregated into health facility, district and regional TB registers/ETR and reported every quarter. The National Tuberculosis and Leprosy Programme (NTLP) compiles the annual TB treatment outcomes from the regional quarterly reports.

4.3.2 Data and statistical analysis

The main outcome measure of the study is the treatment success rate refers to "the proportion of TB cases registered under DOTS between 2004-2015 that successfully completed treatment, whether with bacteriological evidence of success (cured, i.e. smear negative at 5 months) or without (treatment completed)". [28,29] An unsuccessful outcome in this study referred to TB cases recorded as loss-to-follow-up (LTFU), transferred out, failed treatment or died.

Patient level data on treatment outcomes and covariates including: patient demographics, clinical (i.e. disease and laboratory), programmatic (i.e. Facility type, DOTS support, MTP strategy), treatment regimen and treatment outcomes were abstracted from the national Electronic Tuberculosis Register (ETR) by the principal research team. Data were retrospectively abstracted over a 10-year review period (2004/Q3 and 2016/Q1), which coincides with the scale-up to high quality community-based DOTS services in 2005 under the first and second medium-term plans for TB and leprosy in Namibia.

The bacteriological assessment of sputum smears was done at three time points, i.e. baseline, at completion of the intensive TB treatment (i.e. at 2 or 3 months) and at the completion of TB treatment (i.e. at 6 – 8 months). The bacteriological assessment of smears was undertaken by the National Institute of Pathology (NIP), a WHO accredited laboratory that services all DOTS sites in Namibia. The bacteriological results from NIP which were validated by the facility, district and regional TB care teams. Data on treatment outcomes and covariates were exported to RStudio software for statistical analysis.

For the bivariate analyses, missing data on a variable was excluded from the variable. For the regression analyses, a case with missing data values were excluded by list-wise comparisons in SPSS v23. The distribution of missing values for each variable was checked by descriptive frequency analyses and tested for randomness using t-test under missing value analyses. Only variables with missing at random (MAR) were included in the model. Cases of drug resistant tuberculosis and/or missing data on the treatment outcome and/or the covariates of interest (i.e. demographic, clinical and treatment and programmatic records) were excluded from analysis.

The association between patient, programmatic, clinical and treatment covariates with treatment success was determined using bivariate analysis using crude odd ratios (cOR) or Chi-squared test (χ^2). The independent predictors for treatment success were subsequently determined using adjusted odds ratios (aOR) using multivariate logistic regression to control for confounders for treatment outcomes.

The predictors of treatment success are presented as odds ratio (aOR) with a 95% Confidence Interval and at a level of significance (α) set at 0.05).

4.3.3 Ethics

The study was approved by the Research and Ethics Committee of the University of Namibia and the Ministry of Health and Social Services (MoHSS) (MoHSS17/3/3/November 2015) and University of Namibia (SOM/114/2016). The approvals provided for waiver for a written informed consent from the individual TB cases

whose records were included from the ETR data base. In order to maintain confidentiality, data were cleaned and coded to remove any patient specific identifiers such as names and hospital numbers prior to analysis.

4.4 Results

During the review period (2004/ Q3–2016/Q1), a total 104,603 TB cases were registered at 300 DOTS sites in 37 districts in all 14 regions of Namibia. This gives an average of 2,226 (range: 1500 – 3500) cases registered every quarter. The majority of the cases were registered at primary health care facilities (78.9%), predominantly at health centers (62.8%) (Table 1). The number of cases registered by district ranged between 262 and 20,368, with districts in urban, coastal or border settings, such as Khomas, Erongo and Ohangwena regions, registering higher numbers of TB patients (32.3%). The number of TB cases registered per quarter was significantly higher during the implementation of the first medium term plan for tuberculosis (i.e. MTP-I, 2004-2009) than the second (MTP-II, 2005-2010) (Table 1, **Appendix A**).

Most of the cases were male (57.9%), aged between 25-44 years (52.6%) and about half were HIV co-infected (47.9%). Most TB cases were categorized as new (87.6%), i.e. had never received treatment for TB, or had taken treatment for not more than one month, and had pulmonary (PTB, 80.8%) compared to extra pulmonary tuberculosis (EPTB). One third of the cases did not have sputum smear evaluated (33.9%) at the start of TB treatment. Most patients were initiated on 2RHZE/4RH (74.5%) compared to 2RHZE/4RHE. Guardians (i.e. family members or relatives) of the TB cases (48.9%) were the main DOT supporters, compared to DOT nurses or workplace peers.

Figure 2: Period prevalence of TB Treatment outcomes by regions in Namibia

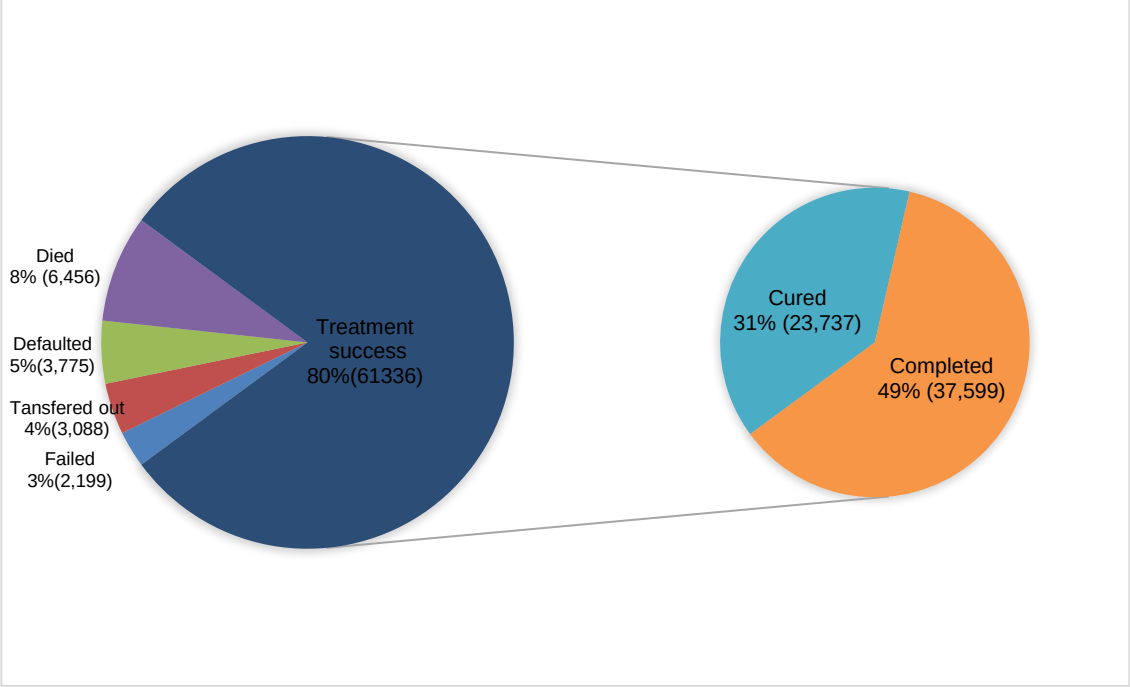

Figure 3: Categories of treatment outcomes (n=76856, not evaluated = 27747)

Of the 104,603 TB cases, 73.5% had treatment outcomes registered in the electronic treatment record. The treatment success rate for the review period was 80% (range: 77.2% - 89.2% by region), which was registered as treatment completion (61.3%) rather than cure (38.7%) (Figure 1). Death and Loss-To-Follow-Up (LTFU) were the most prevalent unsuccessful treatment outcome (Table1). The mean TSR was significantly higher among TB cases registered at primary health care (PHC) facilities (i.e. Health centers, 72.4% and clinics, 74.5%) compared to hospital, 71.4 (p<0.001). Though the TSR were above 80% in most regions (8/14), none of the 14 regions in Namibia achieved the 90% global target for TSR. Only two out of 14 regions, i.e. Zambezi and Omaheke surpassed the 85% WHO TSR targets (Figure 1). Treatment success was statistically significantly (p<0.001) associated with all programmatic, clinical, patient demographic and treatment covariates (Table 1), except for prior exposure to isoniazid prophylactic therapy (IPT, p=0.526) or co-medication with antiretroviral therapy (ART, p<0.127) (Table 1).

Table 1: Univariate analysis of covariates with treatment outcome (n=104603)

Characteristic	**Total (%)**	**Treatment outcome (%)**		**χ^2**	**Cramer's V**	**p-value**
		Successful	**Unsuccessful**			
Regions	**N=76856**	**61338(79.8)**	**15518(20.2)**			
Khomas	15378(20.0)	12105(78.7)	3273(21.3)	393.3	0.07	0.000*
Erongo	9480 (12.3)	7588 (80.0)	1892 (20.0)			
Ohangwena	7520 (9.8)	5903 (78.5)	1617 (21.5)			
Oshikoto	7355 (9.6)	5885 (80.0)	1470 (20.0)			
Kavango West	5595 (7.3)	4335 (77.5)	1260 (22.5)			
Karas	4888 (6.4)	3859 (78.9)	1029 (21.1)			
Otjozondjupa	4638 (6.0)	3698 (79.7)	9402 (20.30)			

Omaheke	3219 (4.2)	2822 (87.7)	397 (12.3)			
Zambezi	3057 (4.0)	2726 (89.2)	331 (10.8)			
Hardap	3069 (4.0)	2522 (82.2)	547 (17.8)			
Kunene	2456 (3.2)	1897 (77.2)	559 (22.8)			
Kavango East	1538 (2.0)	1135 (78.7)	403 (26.2)			
Oshana	1858 (2.4)	1508 (81.2%)	350 18.8%			
Omusati	6805 (8.9)	5355 (78.7%)	145021.3%			
MTP period						
MTP-I	36657	28766(78.5)	7891(21.5)	77.6	0.03	0.000*
MTP-II	40199	32572(81.0)	7627(19.0)			
DOT facility level						
Hospital	16189 (16.1)	12348(76.3)	3841(23.7)	197.0	0.05	0.000*
Health Center	12378 (16.1)	9750(78.8)	2628(21.2)			
Clinic	48289 (62.8)	39240(81.3)	9049(18.7)			
TB registration status						
Previously registered	169 (0.23)	33(19.5)	136(80.5)	382	0.07	0.000*
Patient not registered	76687 (98.8)	61305(79.9)	15382(20.1)			
Gender						
Female	32556(42.1)	26352(80.9)	6204(19.1)	45.1	0.02	0.000*
Male	44300(57.9)	34986(79.0)	9314(21.0)			
Patient's age						
0 - 04 years	4878(6.3)	4191(85.9)	687(14.1)	822.6	0.10	0.000*
05 – 14 years	4167(5.4)	3729(89.5)	438(10.5)			
15 – 24 years	9260(12.1)	7766(83.9)	1494(16.1)			
25 - 34 years	21942(28.6)	17564(80.0)	4378(20.0)			
35 - 44 years	18558(24)	14467(78.5)	3991(21.5)			
45 – 54 years	9462(12.3)	7292(77.1)	2170(22.9)			
55 – 64 years	4498(5.9)	3355(74.6)	1143(25.4)			
65+ years	4091(5.4)	2874(70.3)	1217(29.7)			

Patient aged < 5 years						
Yes	70415(91.6)	5596(86.9)	845(13.1)	218.2	0.05	0.000*
No	6441(8.4)	55742(79.2)	14673(20.8)			
Treatment category*						
New patient	62469(87.6)	51161(81.9)	11308(18.1)	745.4	0.10	0.000*
Retreatment	9567(12.4)	6695(70)	2872(30.0)			
TB case registered						
New patient	62469(81.3)	51161(81.9)	11308(18.1)	1053	0.11	0.000*
Failure	675(0.9)	370(54.8)	305(45.2)			
Previously treated	3508(4.6)	2509(71.5)	999(28.5)			
Readmission	1043(1.4)	674(64.6)	369(35.4)			
Recurrent TB	1313(1.7)	974(74.2)	339(25.8)			
Relapse TB	7848(10.2)	5650(72.0)	2198(28)			
Baseline sputum smear						
Smear negative (-)	14453(18.8)	11544(79.9)	2909(20.1)	9.7	0.01	0.008*
Smear positive (+)	36358(47.3)	29165(80.2)	7193(19.8)			
Smear not done	26042(33.9)	20629(79.2)	5416(20.8)			
Class of smear done						
EPTB No smear	14733(19.2)	11993(81.4)	2740(18.6)	75.3	0.03	0.000*
PTB No smear	13457(17.5)	10423(77.5)	3034(22.5)			
PTB Smear negative (–)	12325(16.0)	9772(79.3)	2553(20.7)			
PTB Smear negative (+)	36341(47.3)	29150(80.2)	7191(19.8)			
Microscopy (Pre-treatment)						
Negative -	15971(20.8)	12832(80.3)	3139(19.7)	9.6	0.01	0.008*
Positive +	34839(45.3)	27876(80.0)	6963(20.0)			
Missing result	26046(33.9)	20630(79.2)	5416(20.8)			
TB Classification						
EPTB	14733(19.2)	11993(81.4)	2740(18.6)	28.7	0.02	0.000*

PTB	62123(80.8)	49345(79.4)	12778(20.6)			
TB regimen initiated						
2HRZE/4HR (A)	57238(74.5)	46673(81.5)	10565(18.5)	1020	0.12	0.000*
2HRZE/1HRZE/5HRE (A)	14006(18.2)	9883(70.6)	4123(29.4)			
2HRZE/1HRZE/5HR (C)	342(0.45)	288(84.2)	54(15.8)			
2HRZ/4HR (C)	4914(6.4)	4251(86.5)	663(13.5)			
Other regimen	356(0.5)	243(68.3)	113(31.7)			
DOT supporter/type						
Guardian (relat/neigh)	28546(48.9)	23480(82.3)	5066(17.7)	201.6	0.06	0.000*
Workplace	682(1.2)	566(83.0)	116(17.0)			
Health Facility	27410(46.9)	21462(78.2)	5948(21.7)			
Community H/Worker	1409(2.4)	1230(87.3)	179(12.7)			
Other	358(0.6)	257(71.8)	101(28.2)			
HIV status						
Negative	25476(44.0)	21752(85.4)	3724(14.6)	652.1	0.11	0.000*
Positive	27704(47.9)	21243(76.7)	6461(23.3)			
Unknown	4676(8.1)	3713(79.4)	963(20.6)			
Patient on HAART						
Yes	16741(62.9)	13184(78.8)	3557(21.2)	2.3	0.01	0.127
No	9894(37.1)	7713(78.0)	2181(22)			
HIV IPT exposure						
Yes	338(3.2)	264(78.1)	74(21.9)	0.4	0.01	0.526
No	10382(96.9)	8256(79.5)	2126(20.5)			
HIV CPT exposure						
No	5065(17.6)	4103(81.0)	962(19.0)			
Yes	23773(82.4)	18382(77.3)	5391(22.7)	33	0.034	0.000*
Developed MDR – TB						
Yes	565(0.6)	-	565(100)	2249.8	0.17	0.000*
No	76291(99.4)	61338(80.4)	14953(19.6)			

Sputum conversion- at 2months						
To smear negative -	17835(49.2)	16735(93.8)	1100(6.2)	12068	0.58	0.000*
Defaulted	478(1.3)	-	478(100)			
Died during treat	1374(3.8)	-	1374(100)			
Remained positive +	2702(7.5)	1971(72.9)	731(27.1)			
Results not available	13306(36.7)	10460(78.6)	2846(21.4)			
Patient transferred	556(1.5)	-	556(100)			
Sputum conversion at 3months						
To smear negative -	25262(69.7)	23663(93.7)	155(6.3)	15587	0.66	0.000*
Defaulted	712(2.0)	-	712(100)			
Died during treat	1543(4.3)	-	1543(100)			
Remained positive +	2361(6.5)	1441(61%)	920(39)			
Results not available	5745(15.9)	4062(70.7)	1683(29.3)			
Patient transferred	628(1.7)	-	628(100)			

** = significant p value by Pearson Chi-Square, IPT= Isoniazid Prophylaxis Therapy, CPT=cotrimoxazole prophylaxis*

*Under the TB programme, patients are categorized as new or retreatment cases. The retreatment cases are further sub-classified as failure, previously treated, readmission, recurrent TB or relapse.

A test of the full logistic regression model (Table 2), against a constant only model was statistically significant, indicating that the programmatic, clinical, patient and treatment predictors as a set reliably distinguished between successful and unsuccessful treatment outcomes (χ^2 = 1401.3, p<0.001 with df = 48). A good relationship between prediction and grouping by successful (1) and unsuccessful outcome (0) was indicated by a

Nagelkerke's R^2 score of 0.597 as well as a non-significant Hosmer and Lemeshow Test ($\chi^2 = 11.9$, p=0.156 with $df = 8$). The prediction success of the model overall was 90.48% with 95.1% for successful treatment outcome and 71.2% for non-successful treatment outcome.

The Wald criterion demonstrated consistency between TB treatment success and the regions of implementation of DOTS in Namibia (p<0.001), the first line TB regimen initiated (p<0.001), the type of DOT provider (p<0.001) with TSR being highest for DOT implemented at the workplace (OR=25.6, 95%CI: 4.3, 151.8), non-conversion of sputum at 2 months (OR=0.2, 95%CI: 0.01, 0.03), co-infection with HIV (OR=0.2, 95%CI: 0.01, 0.5) and exposure to cotrimoxazole prophylaxis therapy (OR=0.4, 95%CI: 0.2, 0.7). Some regions such as Otjozondjupa (OR=2.8, 95%CI:1.3,6.4) had a significantly higher TSR than others. The patients' demographics, health facility level and prior TB registration and/or exposure to TB medication or IPT and diagnostic classifications were not significant predictors for treatment outcomes of tuberculosis. The covariates of the region of the DOTS service, HIV coinfection, TB regimen, and cotrimoxazole prophylaxis and sputum conversion at 2 months were identified as independent predictors for successful treatment outcomes for first line regimens (Table 2).

Table 2: Multivariate analysis of predictors of tuberculosis treatment outcomes

Covariate	Wald	df	OR (95%,CI)	p-value
Medium Term Plan				
MTP-I	0.3	1	1.1(0.8,1.5)	0.608
MTP-II			1	
Region	36.0	13		0.001*
Khomas	2.1	1	2.8(0.7, 11.3)	0.147
Kavango West	1.0	1	0.8(0.4,1.3)	0.324

Zambezi	2.0	1	1.5(0.9,2.6)	0.158
Otjozondjupa	6.3	1	2.8(1.3,6.4)	0.012*
Erongo	1.0	1	0.7(0.3,1.7)	0.328
Karas	0.5	1	0.7(0.3,1.7)	0.465
Hardap	0.7	1	0.4(0.0,3.5)	0.396
Kunene	2.5	1	0.6(0.3,1.1)	0.112
Ohangwena	2.4	1	2.0(0.8,4.9)	0.121
Omaheke	0.8	1	0.7(0.3,1.6)	0.385
Oshikoto	0.0	1	125109200	1.000
Oshana	0.4	1	1.8(0.3,12.5)	0.540
Omusati	1.4	1	1.4(0.8,2.6)	0.237
Kavango East				
Facility level				
Hospital	1.7	2	1.4(0.8, 2.4)	0.428
PHC Clinic	1.1	1	1.3(0.9, 2.0)	0.287
Health Center	1.6	1		0.211
Previously registered				
No	0.1	1	0.6(0.0,9.0)	0.726
Yes				
Patients sex				
Male	1.7	1	0.8(0.6,1.1)	0.197
Female				
TB regimen initiated	41.7	3		0.000*
2 HRZE/4 HR	0.9	1	3.2(0.3,34.5)	0.333
2 HRZES/1 HRZE/5 HRE (Adults)	0.0	1	1.0(0.1,11.1) 1	0.988
2 HRZ / 4 HR				
Diagnostic classification	1.7	2		0.429
Failure	0.5	1	0.7(0.3,1.8)	0.467
Readmission	1.3	1	0.6(0.3,1.4)	0.246
Relapse				
DOT Provider	27.4	4		0.000*
Guardian (relative, neighbor)	25.3	1	10.8(4.3,27.2)	0.000*
Workplace	12.8	1	25.6(4.3,151.8)	0.000*
Health Facility	20.4	1	8.6(3.4,22.0)	0.000*
Community health worker	10.5	1	10.6(2.5,44.4)	0.001*
Other			1	
Patient age category	9.7	7		0.206
0 to 04	2.0	1	7.6(0.5,121.6)	0.153
05 to 14	1.4	1	2.4(0.6,10.5)	0.243
15 to 24	2.0	1	1.6(0.8,3.2)	0.155
25 to 34	3.1	1	1.7(0.9,3.2)	0.080
35 to 44	0.6	1	1.3(0.7,2.4)	0.450
45 to 54	0.3	1	1.2(0.6,2.3)	0.602
55 to 64	3.3	1	2.1(0.9,4.4)	0.070
65+			1	
Sputum not converted	459.1	1	0.02(0.01,0.03)	0.000*
Yes			1	
No				
Sputum conversion 2 months				0.013*

Converted to smear neg	8.7	2	0.7(0.5,1.1)	0.092
Remaining smear pos	2.8	1	0.5(0.3,0.8)	0.005
Defaulted+Died+Transfered+Not available	7.9	1	1	
On ART Treatment	0.8	1	0.8(0.6,1.2)	0.363
No			1	
Yes				
On Cotrimoxazole prophylaxis	9.6	1	0.4(0.2,0.7)	0.002*
No			1	
Yes				
Had IPT (isoniazid) exposure				
No	0.5	1	1.2(0.7,2.6)	0.464
Yes			1	
Current HIV status	26.1	2		0.000*
Negative	0.1	1	1.1(0.5,2.2)	0.813
Positive	12.1	1	0.2(0.1,0.5)	0.001*
Unknown status			1	
Constant	0.000	1	0.121	1.000

Variable(s) entered on step 1: MTP, REGION, FACLEVEL, PREVREGT, SEX1, REGIMENTYPE, DIAGCLASS, SITEINFECTEDTB, MDR Patient, DOTTYPE, PtAgegroup, NOTCONVERTED, SPUTUM2mon, ARTtreat, CPTtherapy, IPTrecieved, HIVSTATUS.

4.5 Discussion

The study determined patient, programmatic and diagnostic predictors of treatment success of first line TB treatment in Namibia (Tables 1). The period prevalence of DOTS treatment success in Namibia was 80%, and varies across the regions in Namibia; this falls short of the global TSR targets to End TB in Namibia.

These findings are consistent with the WHO global tuberculosis reports in LMIC and the National TB and leprosy report for Namibia that depict marginal improvements in past five years[17,29]. However, of concern is that majority of the treatment success end points (61%) in Namibia were due to treatment completion rather than cure. Previous studies in the Omaheke region in Namibia and in other LMIC such as Uganda and South Africa suggest that low acceptance and poor implementation of CB-DOTS as well as social,

cultural, programmatic factors [21,30] and access to DOTS services [31] as important drivers of poor TB treatment outcomes. [18,20,32] This finding suggests the need to strengthen bacteriological monitoring of patients on treatment across all regions in Namibia to optimize case management, as recommended by the global End TB strategy[31].

This study showed significant association between TB treatment success and all programmatic, characteristics such as sex and age, clinical (HIV coinfection, TB diagnosis and sputum conversion at month 2/3) and treatment covariates except IPT and prior ART exposure (Table 1). Similar studies done in South Africa, Uganda [25,26] have also associated poor treatment outcomes to the male gender, HIV co-infection, TB diagnostic class and the sputum conversion at 2 months as well as the WHO TB regimen used[33]; coinfection with HIV and/or diabetes among TB patients; patient related demographic characteristics [34,35]; pharmacokinetic variability among populations. [36] In addition, this study, the poor treatment outcomes were as a result of defaulting of treatment and death. Previous studies have associated high rates of death and defaulting among TB patients to inappropriate choice of TB regimens [3738], HIV co-infection [39,40], adverse drug effects [41–43] and the lack of screening and monitoring systems. [6,18,44,45]

A multivariate logistic regression analysis indicated that the patient's HIV status, TB regimen, the type DOT provider, prior cotrimoxazole prophylaxis, sputum conversion at 2 months and region, were significant predictors of tuberculosis treatment outcomes (Table 2). Our findings differ from other studies which found that patient's demographics including age [41,46] and male-gender [27,46–48 49], TB diagnostic category and level of health facility care were significant predictors of TSR. However, our findings are similar to

others that have reported a positive HIV status and sputum non-conversion at month 2 as important risk factors for poor treatment outcomes.

This study also gives conflicting reports on the effect of gender on TB treatment success compared to a study by Nakiyingi *et al.,* in Uganda that indicated that male patients are at increased risk of poor outcomes [25,26]. However, in our study, patients who received treatment through a work placed based DOTS care increased their TSR by more than three times compared to other types of DOT providers. The results indicate that optimizing the TB regimens [36,41,50], strengthening the support DOTS support system and a system to screen and monitor for risk for poor treatment outcomes among patients with HIV co-infection and prior exposure to cotrimoxazole are equally important considerations to maximize the outcome of DOTS.[36,41,50] The regional variation in TSR may be due to population related characteristics and/or inequitable access to quality of health care at these facilities. We will be exploring this further in future studies.

The fact that bacteriological monitoring is not routinely undertaken in 26% of the TB cases may also predispose patients to poor outcomes. There is also a need to establish the HIV status of the patient as a certain proportion of patients were initiated on treatment with unknown status. There is also a need to establish a system for screening for sub-optimal serum levels of first line regimens as well as pharmacovigilance monitoring [41] given concerns with adverse drug reactions[43] in order to inform appropriate dosage adjustments to improve therapeutic concentrations and/or treatment outcomes. Several studies have shown that up to 75% of the patients do not achieve optimal drug levels and adjustments of doses of TB medications, is likely to improve treatment outcomes. [41,43]

Our findings are also different from a number of other studies that show favourable treatment outcomes among patients on co-medication with antiretroviral drugs (ARVs), isoniazid preventative therapy (IPT) and cotrimoxazole preventative therapy (CPT). These differences may be due to the fact that our study was of a retrospective design that utilized nation-wide routine data compared to RCTs were the conditions of the study are controlled. The regional variation in TSR potentially indicates the heterogeneity of our study population that may have effects on the TSR. We also plan to follow this up in future research studies as the rationale will provide additional guidance on ways to further improve treatment outcomes in Namibia.

We accept this study has a number of limitations. The principal one includes the retrospective design where the accuracy of the data collected cannot be validated and there were missing data on several covariates the and may have bias on interpreting the current results. However, the study gives a true reflection of routine practice in Namibia and describes the limitations of the current DOTS interventions using nation-wide data aggregated over a 10-year period. As a result, we believe that our findings are important in providing evidence to guide efforts to improve treatment outcomes among patients at risk of poor outcomes in the third and future strategic plan for tuberculosis in Namibia.

Acknowledgements

The authors wish to acknowledge the assistance rendered by the staff at the National Tuberculosis and Leprosy Programme, Ministry of Health and Social Services in accessing of the data from TB registers. The authors hereby declare that they have no

conflicts of interest to disclose. This study did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author contributions

DK played the leading role in conceptualizing, data collection, analysis and write up of the manuscript. RN, RA, AT assisted in data collection and cleaning. RV, TR and BG edited and appraised the paper during the various stages of publication. All authors permitted the submission of this paper to this journal.

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NB: The number of dots (•) signify the importance of the reference to this research paper.

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CHATER 5: PATIENT LEVEL MODELING OF LOSS TO FOLLOW-UP OF TB CASES

PREDICTORS OF LOSS TO FOLLOW-UP OF TB CASES UNDER THE DOTS PROGRAMME IN NAMIBIA

Submitted to European Respiratory Journal Open research (ERJ-OR)

Presented at 4th d Medicine Utilization Research in Africa Symposium in conjunction with International society of Pharmacoepidemiology (ISPE), 18-21 June, 2018 University of Namibia Windhoek.

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5.1 Abstract

Setting: In Namibia, one out of every twenty-five cases of tuberculosis is 'lost to follow-up' (LTFU). This has impacted negatively on national efforts to end the disease by 2035. *Objective:* Trends and predictors of lost to follow-up under the DOTS programme in Namibia were determined.

Methods: A retrospective longitudinal analysis of a nation-wide cohort of tuberculosis (TB) cases registered under DOTS programme in Namibia from 2006-2015. The trends and predictors of LTFU among cases in the National Electronic TB Register of the National TB and Leprosy Programme were respectively determined by interrupted time series and multivariate logistic regression analyses using R-Studio software.

Results: Out of 104,203 TB cases, 3775 (3.6%) were LTFU. A quarter (26%) of cases with poor outcomes were due to LTFU. The annual decline in cases LTFU was significant between the first (2005-2010) and second (2010-2015) medium term plan period for TB programme implementation (p=0.002). The independent predictors of LTFU were male sex (p=0.004), 15-24 age group (p=0.03), DOT provider as a group (p<0.001), early phase of TB treatment phase (p=0.047) and living in border/transit regions (p<0.001). HIV coinfection and TB regimen were not significant predictors of LTFU.

Conclusions: There were declining trends in LTFU in Namibia. DOTS programmes should integrate the socio-economic interventions for young and middle-aged adult male TB cases to reduce LTFU.

KEY WORDS: LOSS TO FOLOW-UP, PREDICTORS, TUBERCULOSIS

5.2 Introduction

Tuberculosis (TB) has had a devastating impact on public health in Africa.[1,2] In 2014, out of the 9.6 million cases notified, 28% were from the sub-Saharan countries.[3] Of concern is that the region accounts for 80% of the 1.8 million estimated annual deaths related to TB; this is a disproportionate impact in terms of mortality.[4] Namibia, with a case notification rate of 442 cases per 100,000, is ranked fifth among countries with highest burden of TB.[5,6] However, the universal access to community-based TB care through the Stop-TB and End-TB strategies implemented since 2005 has improved case identification and treatment outcomes in Namibia.[7]

Nevertheless, the gradual rise in incidence of drug resistant TB (DR-TB) and poor treatment outcomes such as 'lost-to-follow-up' (LTFU, i.e. an interruption of TB treatment for at least 2 consecutive months) and death [7–10] are major barriers to ending TB in Namibia. [3,11–13] For instance, the incidence of LTFU among notified cases in Namibia increased from 4% in 2014 to 10% in 2015. Studies in other low and middle-income countries (LMICs) such as India and Malaysia estimate higher incidences of LTFU, 19.2 and 24% respectively. [14,15] In addition, LTFU is an important risk factor for re-emergence of TB strains resistant to first line anti-tuberculosis drugs.[6] In 2014, an estimated 300 000 cases of multi-drug resistant tuberculosis (MDR-TB, i.e. resistance to backbone first line anti-TB medicines, rifampicin and isoniazid) were notified globally.[16] In the same year Namibia notified 137 MDR-TB and 6 extensively-drug resistant tuberculosis (XDR-TB, i.e. MDR-TB with resistance to second line TB drugs, aminoglycosides and/or fluoroquinolones) cases. [17]

The significance of risk factors of LTFU, i.e. patient demographics, socio-economic status, DOTS programme, clinical covariates, TB treatment regimen and HIV co-infection on LTFU have been contested across countries. [14,15,18-25] In Namibia despite universal coverage of high-quality DOTS, little is known about the impact of these factors on poor treatment outcomes and in particular LTFU, hence, the current study intended to determine the prevalence and determinants of LTFU in the Namibian context.

5.3 Methods

5.3.1 Study design and population

The target population were all the new and retreatment cases with drug sensitive TB initiated on first line anti-tuberculosis DOTS regimens. The accessible population were TB cases registered in the National Electronic Tuberculosis Register (ETR) database over a 10 years period, 2006 to 2015. The study included all 104,300 TB cases registered in the ETR; 3775 of these were LTFU. A patient was considered LTFU if TB treatment was interrupted for 2 months or more.[10,16] A retrospective cohort analysis for trends and predictors of LTFU was conducted. Quarterly trends in LTFU of TB cases in Namibia were analysed as a proportion of the total number of TB cases registered for each quarter. The main outcome measure was the effect size (i.e. Odds ratio) for predictors for LTFU compared to TB cases that had a successful treatment outcome (i.e. cured or completed treatment). The study excluded all TB cases whose treatment outcome had not been registered in the ETR at the time of the study and patients with poor treatment outcome other than LTFU, (i.e. died, transferred out, treatment failure) (Figure 1).

5.3.2 Procedure and data analysis

Data on treatment outcome, patient socio-demographic, clinical and treatment characteristics were extracted from the ETR and exported to R-Studio (version 3.3.2) software for quantitative analysis. The main outcome measures were odds ratios of predictors of LTFU, given successful treatment outcome (i.e. cured or completed treatment). The covariates included in the model were patient characteristics, clinical/diagnostic, treatment and DOTS programmatic characteristics. The patient covariates were age, gender, region of residence. The clinical covariates were diagnostic or laboratory classification of the TB case, sputum conversion at two months, and HIV co-infection. The programmatic covariates were the TB strategies implemented (i.e. the first and second Medium-Term Plan (MTP) policy for TB and leprosy), DOT support category and level of health facility.

Other clinical covariates pertained to the treatment regimens and therapy included the DOT regimen initiated, ART regimen, type of DOT provider, and prior prophylaxis with co-trimoxazole preventive therapy (CPT), and isoniazid preventive therapy (IPT). An interrupted time series analysis was performed to determine the changes in level and trend of LTFU among TB cases registered in the DOTS programme during the implementation of the first MTP-I (MTP-I, 2004-2009) and second (MTP-II, 2010-2015) medium term strategies for TB in Namibia. The following segmented regression model was used:

$$Y_t = \beta_0 + \beta_1 * T + \beta_2 * X_t + \beta_3 * T * X_t + e_t$$

Where, Y_t is the outcome, i.e. proportion of patients LTFU at time t, T is the time (in years) elapsed since the start of the study, X_t is a dummy variable indicating the pre-

intervention period (coded 0) or the post-intervention period (coded 1); β_0 estimates the baseline outcome at T=0; β_1 is an estimate of the pre-intervention outcome trend (i.e. the change in outcome with time); β_2 is an estimate of the change in outcome immediately after the intervention, i.e. compared to the outcome at the end of the pre-intervention period; β_3 estimates the change in the post-intervention outcome trend compared to the pre-intervention outcome trend; e_t represents the random variability not explained by the model. Adjustment for serial autocorrelation was carried out by using the Durbin-Watson statistic and by including an autocorrelation parameter in the segmented regression model if necessary.

Bivariate analysis using chi-square test or crude odds ratios was used to identify factors associated with LTFU by comparing patients LTFU against patients with a successful outcome (i.e. cure and/or completed treatment). The significant factors were subsequently included in the multivariate logistic regression analysis to adjust the odds ratios for confounding for independent predictors for LTFU and to elaborate on the relationships between the multiple variables. The level of significance for the bivariate and multivariate analyses was for a 95% confidence interval was set at a type I error alpha (α) of 0.05. For the bivariate analyses, missing data on a variable were excluded from the variable. For the regression analyses, a case with missing data values were excluded by list-wise comparisons in SPSS v23.

The distribution of missing values for each variable was checked by descriptive frequency analyses and tested for randomness using t-test under missing value analyses. Only variables with missing completely at random (MCAR) were included in the model.

5.3.3 Ethics

The research and ethics committees of the Ministry of Health and Social Services (MoHSS17/3/3/November 2015) and University of Namibia (SOM/114/2016) approved the study. The need for written informed patient consent was waived as the study used retrospective records in the electronic TB register (ETR) database. Patient specific identifiers such as names were anonymized or were not extracted or included from the dataset to ensure confidentiality.

5.4 Results

The ITS was performed using prevalence of LTFU registered every quarter (i.e. 3 months, Q1-Q3) by The National TB and Leprosy Programme as aggregated from district and regional data (Figure 1). A significant decline in the quarterly trends in LTFU between 2006 and 2015 of 2.5 cases per quarter ($R^2 = 0.45$) was observed (Figure 2; Table 2). There was a statistically significant decline in the cases LTFU per quarter -0.23% ($p<0.001$) during the first MTP-I. The cases LTFU increased slightly at start of the second MTP-II. The quarterly trend in LTFU significantly increased by 0.16% ($p=0.044$) during MTP-II relative to MTP-I (Figure 1; Table 1).

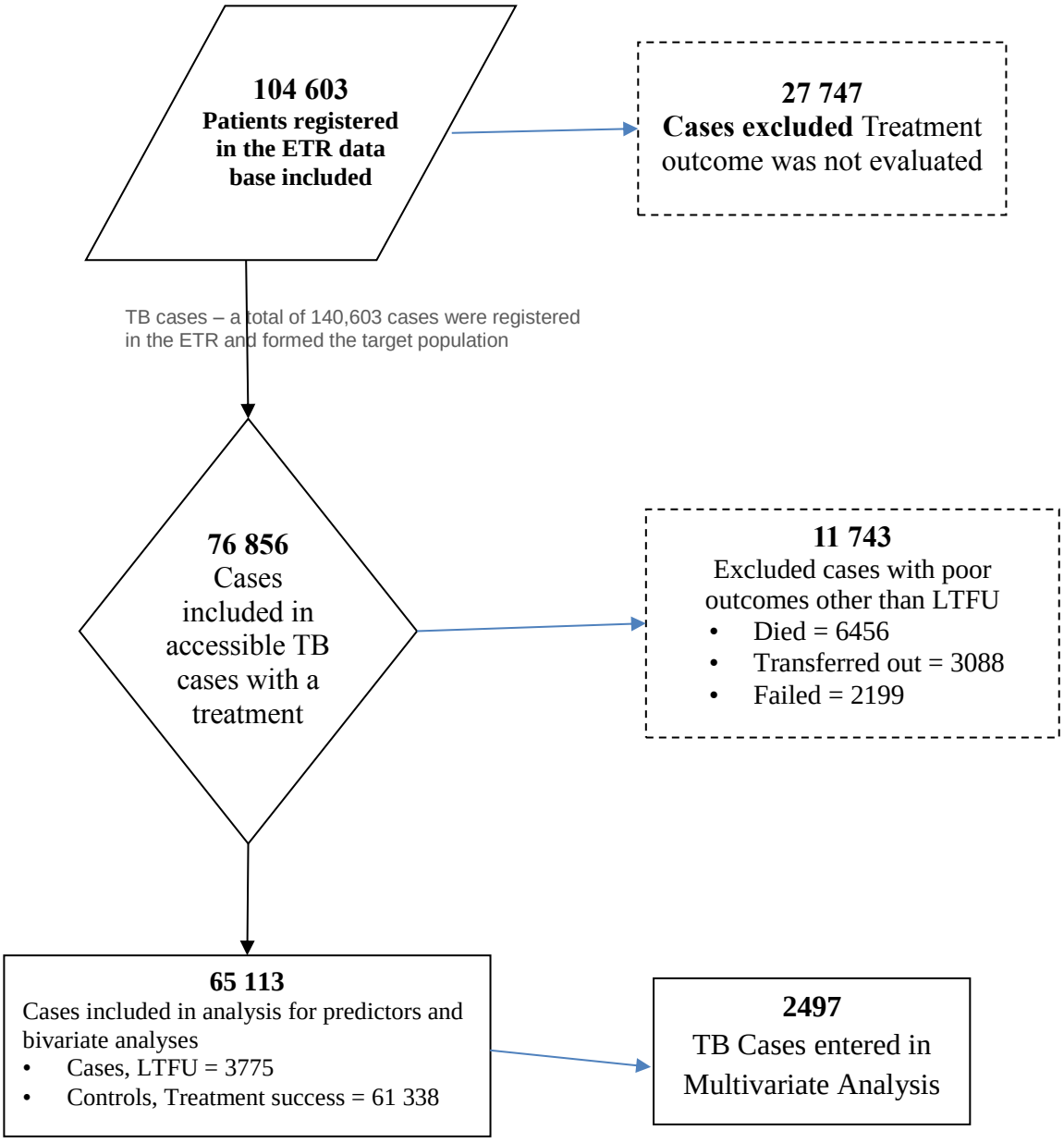

Figure 1 Flow chart: Inclusion criteria of a TB case in the analysis

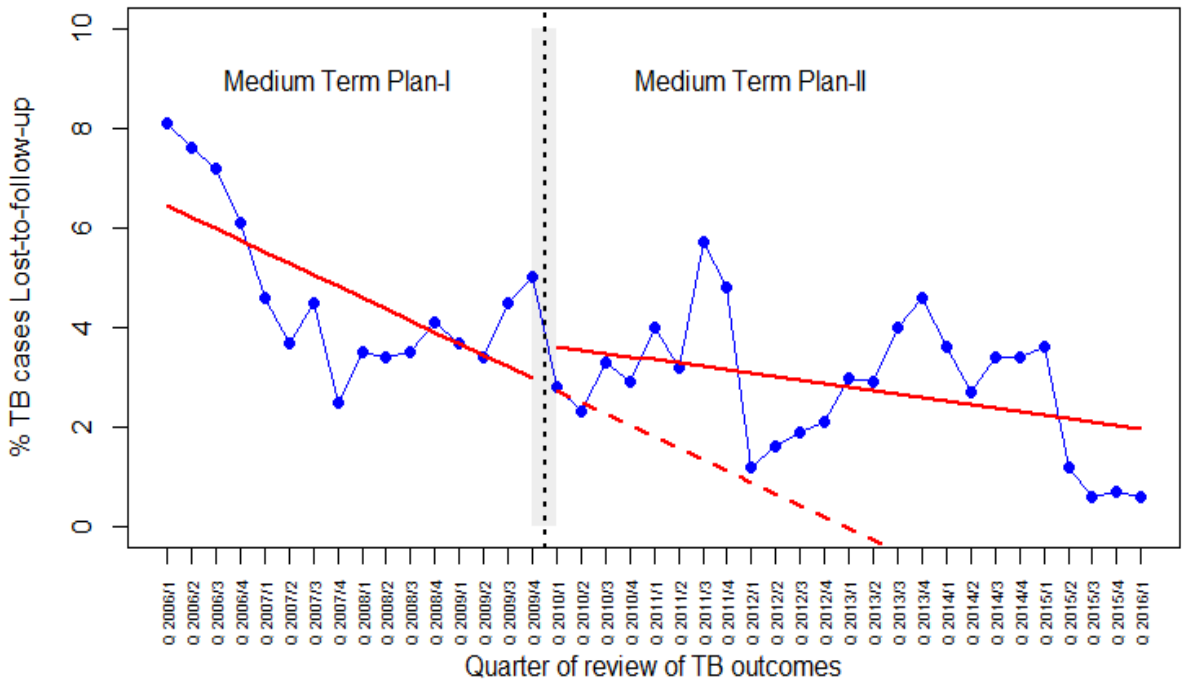

Figure 2: Trends of LFTU cases in Namibia, 2006 - 2015

Out of the 104,603 TB cases registered, 3775 (3.6%) were lost to follow-up**;** this ranged between 0.9%-8.3% by regions in Namibia (Table 2). The prevalence of cases LTFU among patients with unsuccessful treatment outcomes was 24.3% (3775/15,518; Table 2). The majority of patients LTFU were: males (66%), new TB cases (74.4%), aged between 25-34 years (31.7%), registered at PHC clinics (58.6%), with a diagnosis of pulmonary TB (82.4%), initiated on the standard 2HRZ(E)/4HRE regimen (73.6%), registered during the implementation of the first MTP for TB (53.1%) (Figure 3, Table 2).

Table 1: Model for impact of MTP on the LTFU

Coefficients:	Estimate (95% CI)	Std. Error	t value	P-value
Level of LTFU at start of MTP-I (β_0)	6.67(5.33, 8.04)	0.67	9.93	0.0001*
Trend in LTFU in MTP-I (β_1)	-0.23 (-0.37, -0.09)	0.07	-3.32	0.002*
level change in LTFU in MTP-II (β_2)	0.71 (-0.93,2.35)	0.81	0.88	0.385
Trend change in LTFU in MTP-II (β_3)	0.16 (0.004,0.32)	0.08	2.08	0.044*

One third of cases LTFU had TB/HIV co-infection (33.5%) and the majority of sputum smears of LTFU cases were either negative or not evaluated (55.0%) at the start of treatment. A higher number of patients LTFU had a guardian (i.e. family member/relative, neighbor) as the main DOT provider (39.4%; Table 2), were in the continuation phase of treatment (63.73%) and were not taking anti-retroviral treatment (ARVs: 83.9%). The cases LTFU were significantly higher in regions with border, transit, and central business districts such as Khomas and Kunene (p=0.001, Figure 2, Figure 3, Figure 4).

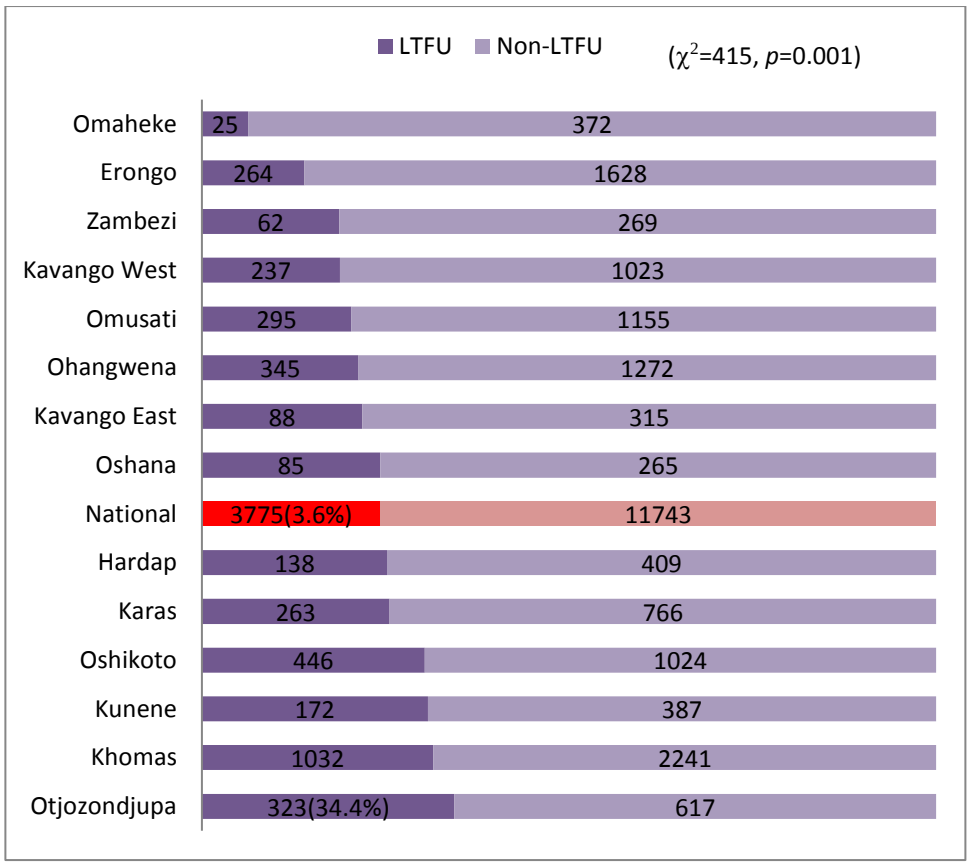

Figure 3: Prevalence of LTFU among TB cases by health regions of Namibia

The bivariate analysis showed a significant association between percentage of cases LTFU and the young/middle-aged adult patients (15-45 years) (p=0.001), male gender (p=0.001) and region where TB care was received (p=0.001), a known HIV status (p= 0.001) and 2-month sputum conversion (p=0.001). The medicine-related characteristics associated with LTFU were: antiretroviral treatment (p= 0.001), a relative being a DOTS provider (p=0.001), type of TB regimen (p= 0.044), MoHSS MTP-I strategic plan (p=0.001), and level of health care facility for TB care (p=0.002) (Table 2).

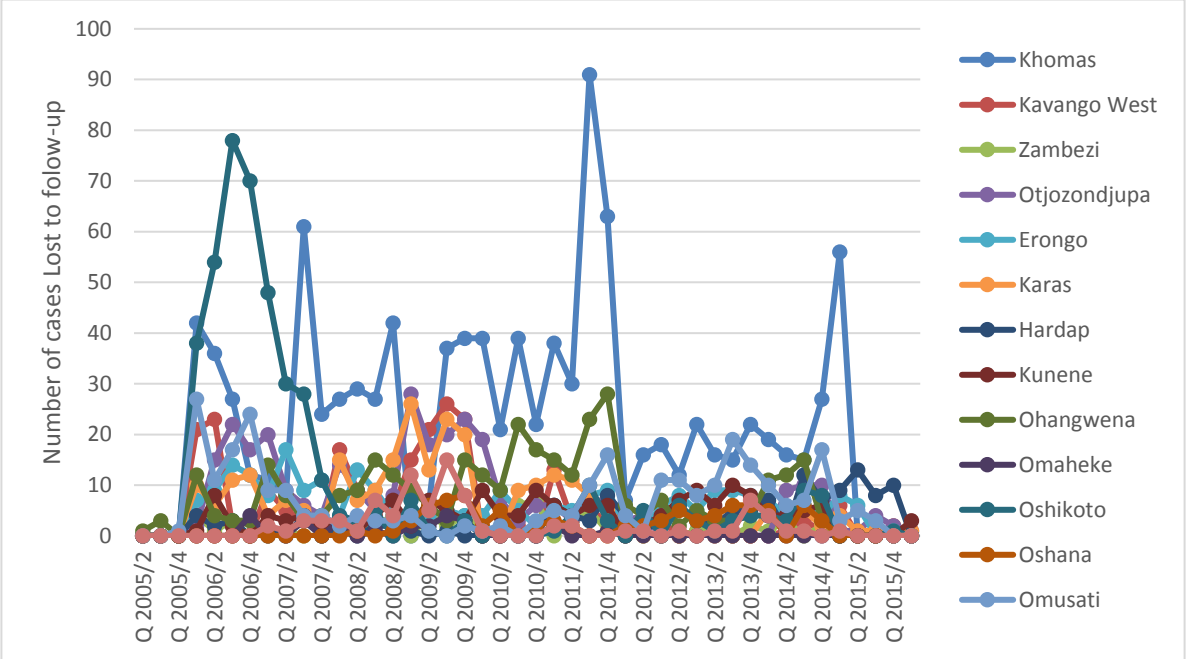

Figure 4 Absolute TB cases lost to follow-up by regions in Namibia

Table 2: Characteristics of the study population

Characteristic	TB treatment outcome		Total	χ^2	df	p-value
	Successful	LTFU				
All TB cases	61338 (94.2%)	3775(5.8%)	65113(100.0%)			
MTP-I	28766 (93.5%)	2005(6.5%)	30771(100.0%)	55.1	1	0.000*
MTP-II	32572 (94.8%)	1770(5.2%)	34342(100.0%)			
Khomas	12105 (92.1%)	1032(7.9%)	13137(100.0%)	474.1	13	0.000*
Kavango West	4335 (94.8%)	237(5.2%)	4572(100.0%)			
Zambezi	2726(97.8%)	62(2.2%)	2788(100.0%)			
Otjozondjupa	3698(92.0%)	323(8.0%)	4021(100.0%)			
Erongo	7588(96.6%)	264(3.4%)	7852(100.0%)			
Karas	3859(93.6%)	263(6.4%)	4122(100.0%)			
Hardap	2522(94.8%)	138(5.2%)	2660(100.0%)			
Kunene	1897(91.7%)	172(8.3%)	2069(100.0%)			

Ohangwena	5903(94.5%)	345(5.5%)	6248(100.0%)			
Omaheke	2822(99.1%)	25(0.9%)	2847(100.0%)			
Oshikoto	5885(93.0%)	446(7.0%)	6331(100.0%)			
Oshana	1508(94.7%)	85(5.3%)	1593(100.0%)			
Omusati	5355(94.8%)	295(5.2%)	5650(100.0%)			
Kavango East	1135(92.8%)	88(7.2%)	1223(100.0%)			
Hospital	12348(92.6%)	986(7.4%)	13334(100.0%)	79.0	2	0.000*
PHC Clinic	39240(94.7%)	2214(5.3%)	41454(100.0%)			
Health Centre	9750(94.4%)	575(5.6%)	10325(100.0%)			
Gender						
Male	34986(93.3%)	2493(6.7%)	37479(100.0%)	117.9	1	0.000*
Female	26352(95.4%)	1282(4.6%)	27634(100.0%)			
Age (years, mean ± SD)	33.5±16.9	33.9±16.4	1.27	65111		0.000*
Age categories (yrs)						
0 to 04	4191(94.8%)	229(5.2%)	4420(100.0%)	29.7	7	0.000*
05 to 14	3729(95.6%)	172(4.4%)	3901(100.0%)			
15 to 24	7766(94.1%)	485(5.9%)	8251(100.0%)			
25 to 34	17564(93.6%)	1196(6.4%	18760(100.0%)			
35 to 44	14567(94.3%)	880(5.7%)	15447(100.0%			
45 to 54	7292(94.3%)	442(5.7%)	7734(00.0%)			
55 to 64	3355(94.6%)	192(5.4%)	3547(100.0%)			
65+	2874(94.1%)	179(5.9%)	3053(100.0%)			
First-line TB regimen						
2 HRZE/4 HRE (Adults)	46673(94.8%)	2553(5.2%)	49226(100.0%)	228.5	4	0.000*
2 HRZES/1 HRZE/5 HRE (Adults)	9883(91.1%)	963(8.9%)	10846(100.0%)			
2 HRZS/1 HRZ/5 HR (Children)	288(94.7%)	16(5.3%)	304(100.0%)			
2 HRZ / 4 HR (Children)	4251(95.0%)	224(5.0%)	4475(100.0%)			
Other Regimens	243(92.7%)	19(7.3%)	262(100.0%)			
Tuberculosis case registered						
New	51162(94.8%)	2794(5.2%)	53956(100.0%)	451.6	5	0.000*

Failure	370(92.0%)	32(8.0%)	402(100.0%)			
Other Previously Treated	2508(90.6%)	261(9.4%)	2769(100.0%)			
Re admission	674(80.0%)	168(20.0%)	842(100.0%)			
Recurrent TB	974(91.1%)	95(8.9%)	1069(100.0%)			
Relapse	5650(93.0%)	425(7.0%)	6075(100.0%)			
New TB case	51162(94.8%	2794(5.2%)	53956(100.0%)	221.1	1	0.000*
Previously treated	10176(91.2%	981(8.8%)	11157(100.0%)			
Pulmonary TB case (PTB)	49345(94.1%)	3109(5.9%)	52454(100.0%)	8.3	1	0.004*
Extrapulmonary TB case (EPTB)	11993(94.7%)	666(5.3%)	12659(100.0%)			
Site of TB infection						
Pulmonary	49165(94.1%)	3108(5.9%)	52273(100.0%)	31.5	6	0.000*
Lymph Nodes	1732(95.9%)	74(4.1%)	1806(100.0%)			
Meningitis	680(93.0%)	51(7.0%)	731(100.0%)			
Miliary	740(94.8%)	41(5.2%)	781(100.0%)			
Other Sites	3295(93.9%)	214(6.1%)	3509(100.0%)			
Pleura	5155(95.5%)	245(4.5%)	5400(100.0%)			
Bones/Joints	571(93.1%)	42(6.9%)	613(100.0%)			
DOT provider						
Guardian (relative, neighbour)	23482(94.0%)	1492(6.0%)	24974(100.0%)	78.6	4	0.000*
Workplace	566(95.6%)	26(4.4%)	592(100.0%)			
Health Facility	21462(95.1%)	1115(4.9%)	22577(100.0%)			
Community health worker	1230(97.5%)	32(2.5%)	1262(100.0%)			
Other	257(87.1%)	38(12.9%)	295(100.0%)			
Baseline sputum smear test						
Smear -	11544(94.1%)	721(5.9%)	12265(100.0%)	10.6	2	0.005*
Smear +	29165(94.5%)	1698(5.5%)	30863(100.0%)			
Smear not done	20629(93.8%)	1356(6.2%)	21985(100.0%)			
Sputum not converted						
Yes	33521(91.2%)	3248(8.8%)	36769(100.0%)	1425.3	1	0.000*
No	27816(98.1%)	527(1.9%)	28343(100.0%)			

Sputum smear month 2						
Converted to smear neg	16735(98.5%)	257(1.5%)	16992(100.0%)	1374.3	2	0.000*
Remaining smear positive	1971(96.5%)	72(3.5%)	2043(100.0%)			
Defaulted+Died+Transfered+ Not available	10460(88.4%)	1369(11.6%	11829(100.0%)			
HIV ART therapy for						
No	7713(93.2%)	563(6.8%)	8276(100.0%)	58.6	1	0.000*
Yes	13184(95.6%)	609(4.4%)	13793(100.0%)			
Exposure to IPT						
Yes	8256(94.8%)	457(5.2%)	8713(100.0%)	2.9	1	0.091
No	264(97.1%)	8(2.9%)	272(100.0%)			
HIV CPT initiated						
No	4103(94.4%)	244(5.6%0	4347(100.0%)	.01	1	0.912
Yes	18382(94.3%)	1102(5.7%)	19484(100.0%)			
HIV status						
Negative	21752(95.7%)	967(4.3%)	22719(100.0%)	90.7	2	0.000*
Positive	21243(94.4%)	1263(5.6%)	22506(100.0%)			
Unknown	3713(92.5%)	299(7.5%)	4012(100.0%)			

A multivariate logistic regression analysis was conducted to identify predictors of LTFU (Table 3). A test of the full model against was statistically significant, indicating that the predictors as a set reliably distinguished between LTFU and a successful treatment outcome (χ^2 = 36.6, p=0.001 with *df* = 15). Nagelkerke's R^2 of 0.35 indicated a relationship between prediction and grouping by LTFU. Prediction success overall was 71.7% (60.8% for LTFU and 79.7% for non-LTFU).

The Wald criterion demonstrated that MTP-II strategy implemented by the National TB and Leprosy Programme (i.e. the number of cases LTFU were 50% lower in MTP-I compared to MTP-II), male gender [18], type of DOT provider [19], a 2 month sputum

conversion; the region in Namibia of DOTS implementation; particularly Otjozondjupa, Karas and Kunene regions; and the young/middle age categories (i.e 15-45 years age) made a significant contribution to prediction of LTFU. However, there was no further significant association of LTFU with HIV status, regimen type and level of DOTS facility.

Table 3: Multivariate logistic regression for predictors of LTFU in Namibia

Covariates	**OR (95% CI)**	**P- value**
Medium term plan for TB		
MTP Period I	0.5 (0.30, 0.96)	0.037*
MTP Period II	1	
Region		0.001*
Karas	18.8(4.9,73)	0.001*
Otjozondjupa	3.9(1.0,15.6)	0.048*
Kunene	3.2(1.0, 4.1)	0.043*
Khomas	1.7(0.13,23)	0.681
Kavango West	1.4(0.5,4.0)	0.491
Zambezi	1.4(0.5,4.0)	0.443
Erongo	0.4 (0.04,3.8)	0.430
Hardap	0.0(0.0,10.4)	1.000
Ohangwena	0.6(0.1,7.3)	0.641
Omaheke	1.6(0.4,2.1)	0.499
Oshikoto	0.0(0.0	0.999
Oshana	0.7(0.7)	0.537
Kavango East	1	

Patients sex		
Male	2.2 (1.3,3.8)	0.004*
Female	1	
Patient Age		0.025*
0 to 04	0.0(0.0, 451)	1.000
5 to 14	14.4(0.5,281)	0.128
15 to 24	29.7(3.1,194)	0.003*
25 to 34	21.6(2.4,110)	0.006*
35 to 44	12.2(1.4,109)	0.025*
45 to 54	11.5(1.2,71.6)	0.033*
55 to 64	6.2(0.6,)	0.140
65+	1	
DOT regimen		
2 RHZE/4 RHE	1.0(0.6,1.9)	0.748
Other regimens	1	
DOT Provider		0.001*
Guardian	1.0 (0.3,4.0)	0.886
Workplace	0.8(0.03,26.8)	0.921
Health facility	0.3(0.08,1.2)	0.085
Community Health Worker	0.0(0.00)	0.999
Other DOTS providers	1	
2 Month's sputum conversion		0.047*
Smear negative	1.6(0.9, 3.2)	0.113
Smear positive	0.4(0.2,1.2)	0.116
Smear not assessed	1	

Anti-retroviral treatment		
No	1.9(0.9,3.9)	0.052
Yes	1	
HIV Status		0.474
Negative	0.8(0.2,3.0)	0.776
Positive	1.5(0.4,6.2)	0.563
Unknown	1	
Facility Level		0.511
Hospital	0.6(0.2,1.9)	0.437
PHC Clinic	0.6(0.3,1.4)	0.247
Health Centre	1	
Constant	0.0	0.006

5.5 Discussion

In the sample taken in this study, of all patients notified in Namibia that had a treatment outcome registered between 2006 and 2016, one out of every 25 TB cases registered was lost to follow-up (Table 2, Figure 2). Furthermore, 1 out of 4 patients with unsuccessful outcomes was a case of LTFU. The prevalence of LTFU varied widely between geographical regions in Namibia, 6.6% to 34%. These are higher than the national (2%) and global benchmarks for LTFU (0%). Studies in other low and middle-income countries in Africa and Asia report the prevalence of LTFU to range between 6% to 24%. [14,20]

This calls for national and regional specific strategies to be incorporated in the medium and long-term strategic plans for TB to reduce the burden of LTFU. The strategy should

target building capacity in tracing and supporting patients at risk of LTFU particularly those registered for DOTS services in border/ transit points as well as regions with central business districts.

Multivariate logistic regression suggested that the TB patients most at risk of LTFU were male patients, young adults (<45 years), cases registered in the capital city, patients in transit and/or close to geographical border DOTS access points with high TB notification rates. Several studies have linked LTFU to patients initiated on therapy at immigration towns like borders and transit points. Similar to our findings, studies associate higher LTFU rates among male patients[21, 20, 24, 28] , the youth or middle aged (34-44 years). [22 15]

Contrary to our findings, Peltzer *et al.*, found no association between LTFU and male gender in a population in South Africa. [25] Nonetheless, young adults in LMICs are a high-risk group for unemployment, HIV, alcohol and drug abuse, smoking, multiple sexual partners that predispose them to TB and poor outcomes such as LTFU.[12-15] The difference in results may be explained from the fact that male patients LTFU in our study were approximately twice higher than the females unlike the previous studies where numbers were comparable. Secondly, the study demonstrated that the clinical risk factors for LTFU were new TB cases, a diagnosis of pulmonary TB (PTB) versus extra pulmonary TB, and sputum conversion at 2 months (i.e. end of the intensive phase of treatment), but not HIV coinfection. Other studies found association of HIV[13] and regimen related ADR[19] with loss to follow-up among TB cases.

The association between LTFU and sputum conversion at 2 months may be due to fact when patient get better, they are less likely to see the need for further treatment hence poor adherence to medication as well as able to be employed in the formal/informal sectors. Thirdly, the programmatic predictors of LTFU were interventions under the respective medium term plan strategy and DOTS support, the MTP-II reduced LTFU by 50% (p=0.037). There was no association between the treatment regimen, ART and prior isoniazid prophylactic therapy (IPT) exposure, HIV status and CPT prophylaxis and the occurrence of LTFU (p>0.05) **(Table 2)**.

Potential limitations of this study should be considered while interpreting the findings. Firstly, the retrospective data had missing information on the treatment outcome for several patients and were excluded from the analysis. However, only variables with a non significant distribution of missing data among the categories were included in the model so as to minimize bias in interpreting the results. In addition, we excluded cases with other poor treatment outcomes (i.e. death, transferred out and failure) as comparisons were made with patients with who had a successful treatment outcome (i.e. cured and completed treatment). There may be many other factors which better explain LTFU including HIV clinical outcomes (i.e. viral load and CD+4 counts) that where not reported in the ETR database used.

Nevertheless, the study utilizes a nation-wide dataset in a high TB burden country over a significant time period (10-year period). This nation-wide study highlights the significance of improving socio-economic welfare of TB patients to abate LTFU as TB is

a disease highly prevalent among patients of low socio-economic backgrounds. Currently strategic goals of the TB programme in Namibia are mainly to case identification and management with limited social-economic interventions among young adults in Namibia.

In conclusion, the study demonstrates a high prevalence LTFU among of TB cases registered under the DOTS programme in Namibia, this is above the global target of 0%. The findings imply that main factors driving LTFU are related to social-economic welfare of young adults who seek temporary employment in regions that provide temporary working opportunities including borders and capital towns. This age group is an important driver for HIV infections in Namibia. The study recommends the integration of socio-economic interventions/incentives in DOTS programmes to support young adult TB cases in informal and/or temporary employments across all regions in Namibia. In addition, there is need for integration of DOTS services in workplaces and institutions that provide temporary employment (e.g. construction sites) for the mobile young male adults to enhance TB treatment continuity of treatment and improve outcomes.

Author contributions

DK played the leading role in conceptualizing, data collection, analysis and write up of the manuscript. AP and MM assisted in conceptualization and data management. RV, TR AP and MM edited and appraised the paper during the various stages of publication. All authors permitted the submission of this paper to this journal.

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CHAPTER 6: PATIENT LEVEL MODELING OF PREDICTORS OF TUBERCULOSIS DEATH RATES

Predictors of Tuberculosis case-fatality under the DOTS programme in a high burden setting.

Submitted to Pharmacoepidemiology and Drug Safety (PDS)
Submitted for oral presentation at 5th d Medicine Utilization Research in Africa Symposium in conjunction with International society of Pharmacoepidemiology (ISPE), 18-21 July, 2019.University of Namibia Windhoek.

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6.1 Abstract

Background: Globally, tuberculosis (TB) is a leading cause of mortality. In 2016, 9.6 million new incident cases of TB were notified, leading to 1.8 million deaths. In 2017, Namibia with a population of 2.3 million recorded 700 deaths due to TB. However, there is limited data on predictors of death under the DOTS programme.

Aim: The predictors of death among TB cases registered under the DOTS programme in Namibia were explored.

Methods: We conducted two case-control studies using hospital-based data and national electronic TB register (ETR). Cases were all patients with treatment outcome of death and the controls, as successful outcome. Data on treatment outcomes, patient and clinical covariates were abstracted from the TB register for at Katutura intermediate Hospital, Windhoek (January 2016 – June 2018) and the national ETR (2005-2015). The patient socio-demographic, clinical and treatment predictors of TB case-fatality were determined using multivariate logistic regression to determine the odd ratio (OR) for death using SPSS v23 software.

Results: Of the 124 subjects included in the hospital-based study, 54.8 %(n=68) were cases (i.e. died) death compared to 45.2% controls, (i.e. patients cured of TB). Similarly, of the 67794 subjects included in the national ETR based study, 9.5 %(n=6456) were cases compared to controls (i.e. successful outcome). The independent predictors of TB case-fatality under the DOTS programme were a negative HIV status OR=0.2 (95%CI:

0.1, 0.4, p=0.001) and the non-assessment of drug resistant testing using a GeneXpert, OR=3.4 (95%CI: 1.6, 7.5, p=0.003). The national ETR analysis also showed that the region of DOTS implementation (p<0.001), patients age (p<0.001) and patients without cotrimoxazole prophylaxis (p=0.013) as independent predictors of death.

Conclusion: Clinical and diagnostic factors including HIV co-infection and related factors such as co-trimoxazole and lack of sputum and/or drug-resistance testing may be predictors for death among patients treated under the DOTS programme in Namibia. This calls for strengthening and strict clinical monitoring among patients initiated on DOTS to minimize deaths among TB patients.

KEY WORDS: DEATH, DOTS, NAMIBIA, PREDICTORS, TUBERCULOSIS

6.2 Introduction

Tuberculosis (TB) remains one of the world's biggest public health threats and ranks alongside HIV (i.e. Human immunodeficiency virus) as the world's leading cause of death from an infectious disease.[1,2] For instance, the World Health Organisation (WHO) estimated about 9.6 million new cases of TB globally, that led to 1.8 million death in 2016.[3,4] Moreover, a significant number of the TB associated deaths (0.4 million) were among patients with co-infected with HIV. [5]

Moreover 21% of the new cases notified (i.e. 281 cases per 100,000 population) were from the African region, and is more than double the global average (i.e. 133 cases per 100,000 population).[6] The WHO ranks Namibia 5th, among the top 30 high TB burden settings in the world.[7–9] In 2017 alone Namibia with an estimated population of 2.3 million notified over 8 800 new infections (i.e. case notification rate (CNR) of 446 cases per 100 000 persons), and 700 deaths from TB-related infections.[9] Indeed, death rates are unacceptably high given that they are preventable and TB treatment has up to 98% cure rate.[10,11]

In contrast to high case-fatality among TB patients, the implementation of high quality DOTS programme in 2005 in Namibia has markedly improved tuberculosis treatment outcomes including reduction in annual death rate. [5,12] Similarly, since the implementation of the Millennium Development Goals (MDGs), the incidence of TB has declined by 18% world-wide and prevented an over 4.6-6.3 million deaths related to TB. [5,13–15] In 2015, Namibia achieved universal access to DOTS services, i.e. patients receive TB care and medications without co-payment and the services are accessible in all the 14 regions of Namibia.[12,16]

HIV co-infection among TB patients is linked to poor prognostic outcomes including death, particularly among patients in low and middle-income countries (LMICs). [5,11,17] This is a major concern given that over 38% of TB patients in Namibia have HIV co-infection, and is among the highest globally [18] . Also, the death rate among TB patients varies widely among the 14 geographical regions of Namibia, with the Khomas region

(i.e. capital region of Namibia) and Kavango region (i.e. region with highest poverty rates in Namibia) the most affected.[18,19]

Little is known of the impact of clinical, patient socio-demographic[19], programmatic and treatment factors on death rates among TB patients on the under DOTS in Namibia. [5,20] The current high death rate among patients on the DOTS programme in Namibia may stigmatize patients and/or communities, reduce adherence to treatment, and affect negatively the health seeking behaviours and treatment and public health outcomes.[6,21,22] In view of this, there is a need for policy and clinical guidance on risk prevention of TB associated case-fatalities in the DOTS programme in Namibia. Consequently, the aim of the study was to explore the determinants of death among patients registered under the DOTS programme in Namibia.

6.3 Methods

6.3.1 Design and study population

Two case-control designs were conducted to determine the predictors of death, i.e. a hospital-based study among TB patients initiated on first line DOTS regimens in the Khomas region of Namibia and the national electronic TB register (ETR).

A hospital-based study was conducted in Khomas region to gain access to patient clinical records to collect data on sociodemographic (e.g. alcohol intake and smoking), clinical (e.g. laboratory results such as drug resistance testing) covariates not captured in the national

ETR that would impact on death outcome. Quantitative data such as patient clinical, treatment and demographic characteristics were abstracted from the patient TB registers, treatment cards as well as the ETR database. The cases were all patients whose treatment outcome was registered as death (i.e. a patient who died of TB or for any other reason during the course of treatment) after initiating DOT. The controls were patients who had a successful treatment outcome registered as cured (i.e. Patients whose sputum smear tested negative after the completion of treatment) at the hospital, and patients with a successful treatment outcome for the national data-based study.

The target population included all TB patients initiated on the first line DOTS regimen under the DOTS programme of the Khomas region Windhoek Namibia during the study period of March 2018 to June 2018 for the hospital based study as well as cases registered in the nation ETR database from 2004 to 2016. The accessible population were patients whose treatment outcome was entered in the regional and/or national TB register at the time of study. Over a thousand cases of TB are registered each year in the Khomas region and approximately 5% of the patients die during TB treatment. The national database has a total 104603 patients registered from 2004-2016, 5% of who are estimated to die while on DOT treatment. The study included only TB patients on first line DOTS regimens and a treatment outcome registered as either death or successful (i.e. cured or completed treatment) irrespective of their demographic or clinical characteristics. The study excluded cases with missing data on treatment outcomes and/or covariates from the analysis.

For the hospital-based study, a stratified simple random sampling method was used to select cases (i.e. patients that died) and controls (i.e. patients cured from TB). After identifying the cases in the hospital based study, the controls were randomly selected from the hospital register and matched with the case based on the HIV status (i.e. that is 1:1 matching) to predict odds death. For the hospital-based study, 68 cases (i.e. deaths) and 56 controls (i.e. patients cured of TB) were randomly included in the study. For the ETR data-based study, all the 4863 cases (died) and 46708 controls (successful treatment) were included in unmatched case-control for analysis.

6.3.2 Data collection procedure

For the hospital based study, an abstraction tool (Appendix B), was used to collect data treatment outcome, patient socio-demographics (e.g. age, gender, alcohol use, residence, education level and smoking), clinical (e.g. category of TB, co-infections and diagnostic tests) and treatment (e.g. TB regimen and co-medications) covariates. The data abstraction tool was face validated by the Khomas regional coordinator for TB of Ministry of Health and Social services and an academic supervisor at the University of Namibia. The abstraction tool was subsequently tested on five clinical records at TB hospital and was standardized prior to the collection of data. Data were abstracted from the patients' treatment cards and the region TB register by the researchers (DK and AS). The clinical files were from five facilities in the Khomas region, the TB hospital of Intermediate Katutura Hospital (IHK) and four clinics (i.e. Wanaheda, Okuryangava, Hakahana and Katutura Health Center) over a 3-month period, March-June 2018. Data from the ETR were exported to SPPS software v23 for management and normality testing prior to analysis

6.3.3 Data analysis

The main outcomes of the study were odds of death among patients on first line DOT regimens and the predictor variables included patient socio-demographic, clinical and treatment characteristics. The data were double entered in Epidata v 3.1 software by the two researchers (DK and AS) for management (i.e. to check for errors, duplication and outliers in the variables such as age). Data were then exported to SPSS v23 software for quantitative analysis.

Descriptive statistical analysis was used to determine the rate of death among TB patients on first line DOT by the respective demographic, clinical and treatment characteristics. The factors associated with death among TB patients under the DOTS programme were determined by bivariate analysis (i.e. chi-square test for categorical variables and student t-test for continuous variables). Multivariable binary logistic regression analysis was used to determine the crude odds ratios (cOR) for the death outcome relative to cured or treatment success. For all statistical tests, the level of significance (alpha) was set at <0.05.

For the bivariate analyses, missing data on a variable were excluded from the variable. For the regression analyses, a case with missing data values were excluded by list-wise comparisons in SPSS v23. The distribution of missing values for each variable was checked by descriptive frequency analyses and tested for randomness using t-test under missing

value analyses. Only variables with missing completely at random (MCAR) were included in the model.

6.3.4 Ethics

Ethical clearance for the study was obtained from the research and ethics review board (REC) of the Ministry of Health and Social Services (MoHSS17/3/3/November 2015) and the research ethics committees of Katutura Intermediate Hospital as well as the University of Namibia (SOM/114/2016). Waiver for informed consent was given since the study was based on retrospective patient records. Confidentiality of the patients' information was kept by use of codes in place of patient identifiers and no third parties were directly involved in handling of the data. All patient records and data were kept in a locked cabinet in a lockable office, on a security-controlled campus at the School of Pharmacy, University of Namibia.

6.4 Results

6.4.1 Hospital-based study: Univariate analysis of factors associated with death

Of the 3647, TB patients notified in the Khomas region during the study period (i.e. January 2016 to April 2018), 96 deaths were registered. Of the 124 patients included in this study, 54.8% (n=68) were cases (i.e. died) and 56 were controls (i.e. cured of TB) were selected as controls. The majority of the patients were male (67.6%), lived in Katutura, a suburb of Windhoek (96%), and received TB care at primary health care facilities. Of the 124 patients, 97.3% were new TB infections, 80.6% had pulmonary tuberculosis (PTB) and 69.4% had a positive sputum smear test. About half (50.6%) of

all patients (i.e. cases and controls) were co-infected with HIV and 90.47% of these were on first line HAART regimen (Table 1).

The clinical factors that were significantly associated with death in the DOTS programme were HIV coinfection (p<0.001), PTB versus extra pulmonary TB (EPTB) (p<0.001) and baseline sputum smear test (p<0.001). The primary DOT provider was also significantly associated with death outcome (p=0.003). Smoking status (p<0.001) and patient occupation (p=0.003) were significantly associated with death. There was no association between death and patients' gender or age as well as the DOT treatment (p>0.05) (Table 1 and 2).

Table 1: Univariate analysis of factors associated death of TB patients at hospital level (n=124)

Predictors	**Total (%)**	**Treatment outcome (%)**		χ^2	p-value
		Died	Successful		
All cases	124	68(54.8%)	56(45.2%)		
Patient's sex					
Male	79 (63.7)	46 (67.6)	36(45.6)	1 (0.4)	0.552
Female	45(36.3)	22(32.4)	23(51.1)		
Residential address					
Windhoek west	3.(2.4)	2(66.7)	1(33.3)		
Windhoek north	1(0.8)	1(100)	_	3(2.2)	0.547
Windhoek central	1(0.8)	1(100)	_		
Katutura	119(96.0)	61(51.3)	58(48.7)		
Employment					
Self-employed	2(1.6)	2 (3.2)	-	2(11.9)	0.003*
Unemployed	13(10.5)	12 (19.0)	1(1.7)		
Unknown	109(87.9)	49(77.8)	58(98.3)		
Alcohol use					
Yes	11(8.9)	11 (17.5)	-	3 (27.8)	0.000*
No	15(12.1)	14.2(22.2)	1 (1.7)		

Unknown	98(79)	37(58.7)	58 (98.3)		
Smoking					
Yes	3(2.4)	3 (4.8)	-	3(26.3)	0.000*
No	22(17.7)	21 (33.3)	1 (1.7)		
Unknown	99((79.9)	38 (60.3)	58 (98.3)		
Health facility					
Primary health care	84(67.7)	46 (54.8)	38(45.2)	1(0.6)	0.449
Hospital	40(32.3)	19(47.5)	21(52.5)		
DOT provider					
Health facility	82(66.1)	39 (47.6)	43 (52.4)	4 (15.7)	0.003*
Guardian	24(19.4)	10 (41.7)	14 (58.3)		
Neighbor	1 (0.8)	-	1 (50)		
Workplace	2(1.61)	1 (50)	1 (50)		
Community worker	14(11.3)	-	14 (100)		
Type of TB					
Pulmonary TB	100(80.6)	41 (63.1)	59 (10 0)	1(27.01)	0.000*
EPTB	24(19.4)	24 (39.9	-		
Diagnostic smear					0.000*
Smear positive	86(69.4)	27 (41.5)	59 (100)	2(29.7)	
Smear negative	12(9.7)	12 (18.5)	-		
Smear not done	26(21)	26 (40.0)	-		
Treatment after failure					
Relapse	20(16.2)	14 (87.5)	5 (100)	2(0.69)	0.708
Lost to follow up	1(0.8)	1 (6.3)			
GeneXpert results					
XpertMTB/Rif +ve	41(33.3)	29(44.6)	12 (20.7)	2(10.2)	0.006*
XpertMTB/Rif -ve	7(5.6)	5(7.7)	2(3.4)		
Not done	75(60.5	31 (47.7	44 (75.9)		
Diagnostic type					
New TB case	107(97.3)	52(94.5)	53 (96.4)	2 (5.0)	0.082
Treatment failure	3(2.7)	3 (5.5	2 (3.6		
HIV status					
Negative	59(47.6)	18(27.7)	41(69.5)	2(22.3)	0.000*
Positive	63(50.8)	45(69.2)	18(30.5)		
Unknown	2(1.6)	2(3.1)	_		
HAART regimen					
TDF/3TC/EFV	57(90.3)	39(86.7)	19(100)	2 (2.8)	0.247
ABC/3TC/EFV	3(4.7)	3(6.7)	_		
Others	3(4.7)	3(6.7)	_		

On CPT					
Yes	63(50.8)	46 (97.9)	19(100)	1(0.4)	0.522

CPT = cotrimoxazole prophylactic, therapy, HAART = highly active antiretroviral therapy, GeneXpert =TB diagnosis and TB resistance testing

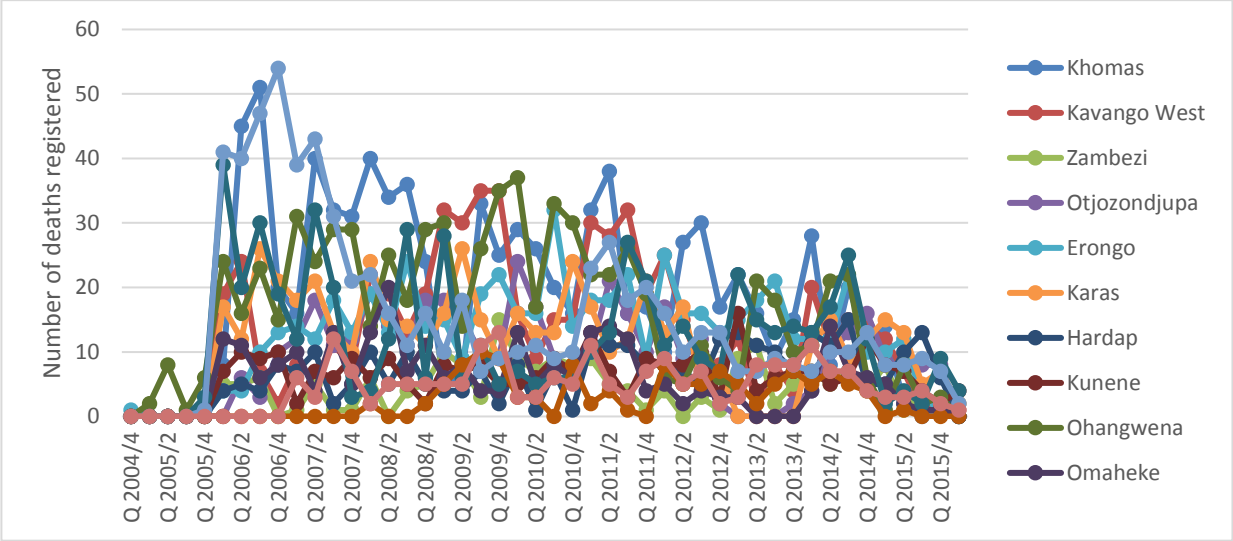

Figure 1 Nation-wide quarterly trends in TB deaths under the DOTS programme by region

The trends in the death rates among TB patients under the DOTS programme are declining and range between 0-55 deaths per quarter (i.e. every three months). The Khomas region, Kavango east Ohangwena, Karas and Erongo region have higher deaths registered per quarter (Figure 1).

6.4.2 Nation-wide study: univariate analysis of factors associated with death

The programmatic factors that are significantly (p<0.001) associated with TB case-fatality under the national TB programme geopolitical region of implementation of the DOTS programme and the DOT supporter. The patient demographic factors associate with death were age (p<0.001) but not gender (p=0.116). The clinical factors associated with death were HIV co-infection, the diagnostic classification of TB by site of infection, transfer status and type of patient (i.e. new or retreatment) and bacteriological testing at 2 months.

The treatment factors associate with deaths were co-trimoxazole prophylaxis and the first line DOTS regimen (Table 2).

Table 2 Nation-wide study: univariate analysis of factors associated with death

Characteristic	TB treatment outcome		Total	χ^2	df	p-value
	Successful	Died				
All TB cases	61338 (90.5%)	6456(9.5%)	67794(100%)			
TB strategic plan implemented						
MTP-I	28766(90.4%)	3053(9.6%)	31819(100.0%)	0.4	1	0.548
MTP-II	32572(90.5%)	3403(9.5%)	35975(100.0%)			
Region of DOTS implementation						
Khomas	12105(93.3%)	871(6.7%)	12976(100.0%)			
Kavango West	4335(87.5%)	619(12.5%)	4954(100.0%)			
Zambezi	2726(93.2%)	199(6.8%)	2925(100.0%)			
Otjozondjupa	3698(89.9%)	417(10.1%)	4115(100.0%)			
Erongo	7588(92.8%)	589(7.2%)	8177(100.0%)			
Karas	3859(88.0%)	525(12.0%)	4384(100.0%)			
Hardap	2522(89.3%)	301(10.7%)	2823(100.0%)	452.5	13	0.000*
Kunene	1897(86.9%)	286(13.1%)	2183(100.0%)			
Ohangwena	5903(88.6%)	760(11.4%)	6663(100.0%)			
Omaheke	2822(91.1%)	274(8.9%)	3096(100.0%)			
Oshikoto	5885(91.2%)	567(8.8%)	6452(100.0%)			
Oshana	1508(92.5%)	123(7.5%)	1631(100.0%)			
Omusati	5355(88.3%)	711(11.7%)	6066(100.0%)			
Kavango East	1135(84.1%)	214(15.9%)	1349(100.0%)			
Health facility						
Hospital	12348(88.2%	1647(11.8%)	13995(100.0%)			
PHC Clinic	39240(91.1%	3851(8.9%)	43091(100.0%)	103.2	2	0.000*
Health Centre	9750(91.1%	958(8.9%)	10708(100.0%)			
Gender						
Male	34986(90.3%	3748(9.7%)	38734(100.0%)	2.5	1	0.116
Female	26352(90.7%	2708(9.3%)	29060(100.0%)			
Mean age (yrs ±SD)	33.5±16.9	42.5±18.2				0.000*
Age categories (yrs)						
0 to 04	4191(94.9%)	225(5.1%)	4416(100.0%)			
05 to 14	3729(97.0%)	114(3.0%)	3843(100.0%)			
15 to 24	7766(95.4%)	378(4.6%)	8144(100.0%)			
25 to 34	17564(92.2%)	1495(7.8%)	19059(100.0%)	1625.9	7	0.000*
35 to 44	14567(89.6%)	1682(10.4%)	16249(100.0%)			
45 to 54	7292(87.3%)	1062(12.7%)	8354(100.0%)			
55 to 64	3355(83.0%)	686(17.0%)	4041(100.0%)			
65+	2874(77.9%)	814(22.1%)	3688(100.0%)			
First-line TB regimen						
2 HRZE/4 HRE (Adults)	46673(91.2%)	4504(8.8%)	51177(100.0%)			
2 HRZES/1 HRZE/5 HRE (Adults)	9883(85.5%)	1679(14.5%)	11562(100.0%)			
2 HRZS/1 HRZ/5 HR (Children)	288(94.1%)	18(5.9%)	306(100.0%)	541.2	4	0.000*
2 HRZ / 4 HR (Children)	4251(95.6%)	196(4.4%)	4447(100.0%)			
Other Regimens	243(80.5%)	59(19.5%)	302(100.0%)			
Tuberculosis case registered						
New	51162(91.5%)	4751(8.5%)	55913(100.0%)			
Failure	370(87.1%)	55(12.9%)	425(100.0%)			
Other Previously Treated	2508(82.3%)	541(17.7%)	3049(100.0%)	466.5	5	0.000*
Re admission	674(85.1%)	118(14.9%)	792(100.0%)			
Recurrent TB	974(83.5%)	192(16.5%)	1166(100.0%)			
Relapse	5650(87.6%)	799(12.4%)	6449(100.0%)			
TB case						
New TB case	51162(91.5%)	4751(8.5%)	55913(100.0%)	389.7	1	0.000*
Previously treated	10176(85.6%	1705(14.4%)	11881(100.0%)			

Pulmonary TB case (PTB) Extrapulmonary TB case (EPTB)	4934590.6%) 11993(89.8%)	5093(9.4%) 1363(10.2%)	54438(100.0%) 13356(100.0%)	8.9	1	0.003*
Site of TB infection Pulmonary Lymph Nodes Meningitis Miliary Other Sites Pleura Bones/Joints	49165(90.6%) 1732(94.9%) 680(79.3%) 740(85.8%) 3295(89.0%) 5155(90.6%) 571(93.0%)	5079(9.4%) 93(5.1%) 178(20.7%) 122(14.2%) 408(11.0%) 533(9.4%) 43(7.0%)	54244(100.0%) 1825(100.0%) 858(100.0%) 862(100.0%) 3703(100.0%) 5688(100.0%) 614(100.0%)	204.3	6	0.000*
DOT provider Guardian (relative, neighbour) Workplace Health Facility Community health worker Other	23482(92.0%) 566(91.9%) 21462(89.1%) 1230(95.1%) 257(86.5%)	2038(8.0%) 50(8.1%) 2625(10.9%) 64(4.9%) 40(13.5%)	25520(100.0%) 616(100.0%) 24087(100.0%) 1294(100.0% 297(100.0%)	161.4	4	0.000*
Baseline sputum smear test Smear - Smear + Smear not done	11544(87.7%) 29165(92.5%) 20629(89.3%)	1615(12.3%) 2359(7.5%) 2482(10.7%)	13159(100.0%) 31524(100.0%) 23111(100.0%)	307.4	2	0.000*
Sputum not converted Yes No	33521(84.8%) 27816(98.4%)	5991(15.2%) 465(1.6%)	39512(100.0% 28281(100.0%)	3495.9	1	0.000*
Sputum smear month 2 Converted to smear negative Remaining smear positive Defaulted+Transfered+Not available	16735(98.5%) 1971(95.4%) 10460(84.3%)	256(1.5%) 94(4.6%) 1950(15.7%)	16991(100.0%) 2065(100.0%) 12410(100.0%)	2161.2	2	0.000*
On ART therapy No Yes	7713(88.2%) 13184(87.8%)	1030(11.8%) 1828(12.2%)	8743(100.0%) 15012(100.0%)	0.8	1	0.365
Exposure to IPT Yes No	8256(87.8%) 264(86.6%)	1142(12.2% 41(13.4%)	9398(100.0%) 305(100.0%)	0.5	1	0.498
HIV CPT initiated No Yes	4103(90.0%) 18382(87.3%)	454(10.0%) 2684(12.7%)	4557(100.0%) 21066(100.0%)	26.9	1	0.000*
HIV status Positive Negative Unknown	21752(94.5%) 21243(86.8%) 3713(91.3%)	1272(5.5%) 3236(13.2%) 355(8.7%)	23024(100.0%) 24479(100.0%) 4068(100.0%)	825.1	2	0.000*
Transferred in Yes Out	0(0.0%) 61338(90.6%)	127(100.0% 6329(9.4%)	127(100.0%) 67667(100.0%)	1208.9	1	0.000*

6.4.3

Hospital-based study: Predictors of death outcome among TB cases

The multivariate logistics model for variables associated with death suggested that HIV co-infection and access GeneXpert® testing (i.e. confirmation of mycobacterium and rifampicin resistance) as independent predictor of death. The model suggests that patients infected with HIV and patients without bacteriological and/or drug resistance testing are more likely to die from TB under the DOTS programme (Table 3). A relationship between prediction and grouping by death (1) and cured (0) indicated significance between death

on DOTS and HIV negative test (OR=0.2, 95%CI: 0.1, 0.4), and positive GeneXpert not done (OR=3.4, 95%CI: 1.6, 7.5). Thus, HIV coinfection and bacteriological and/or drug resistance testing were identified as independent risk factors for death in the DOTS programme in Namibia (Table 3). Demographic and programmatic factors were not independent predictors of death in the DOTS programme.

Table 3: Predictors of death outcome among TB cases on DOT for hospital based study

Predictors of death	B	Standard error	Wald	df	OR (95% CI)	p-value
HIV status						
HIV negative	-1.739	0.397	19.18	1	0.2(0.1,0.4)	0.000*
HIV positive					1	
GeneXpert test						
Not done	1.238	0.395	9.828	1	3.4(1.6,7.5)	0.002*
Done					1	
Patient sex						
Female	-0.222	0.374	0.353	1	0.8(0.4, 1.7)	0.553
Male					1	
Type of TB						
Pulmonary TB	21.99	11602.714	0.000	1	0.000	0.998
EPTB					1	
Sputum test						
Positive (+)	-21.99	11602.714	0.000	1	0.000	0.998
Negative (-)						
Health facility						
PHC facility	0.201	0.385	0.572	1	1.4(0.6,2.8)	0.450
Hospital					1	

PHC = Primary healthcare facility (i.e., clinic and health center)

6.4.4 Nation-wide predictors of death of TB cases under the DOTS programme

A multivariate logistic regression analysis was conducted to identify predictors of TB case-fatality based on nation-wide data (Table 4). Of the 2644 patients included in the logistic analysis, 250 death cases and 2394 controls met the inclusion criteria for predictors of TB case fatality in Namibia. A test of the full model against a constant only

model was statistically significant, indicating that the predictors as a set reliably distinguished between case-fatality and successful outcome (χ^2=394.9, DF=29, p<0.001).

Nagelkerke's R^2 of 0.30 indicated a relationship between prediction and grouping by death. Prediction success overall was 91.1% (91.1 for successful outcome and 10.8% for death of a TB case). The Wald criterion demonstrated that the higher the patient's age (p<0.001), the DOT provider, sputum non-conversion at month 2 of treatment, the region in Namibia of DOTS implementation particularly Khomas region and Zambezi regions and Omusati regions, HIV co-infection (p<0.001) and CPT prophylactic therapy (p<0.013) made a significant contribution to prediction of death among TB patients. However, there no significant impact of the patient gender, regimen type, MTP and facility level on death (Table 4).

Table 4 Nation-wide predictors of TB case-fatality under the DOTS programme

Covariate	**B - coefficient**	**Standard error**	**Wald**	**df**	**OR (95%CI)**	**p-value**
Geographical region			49.3	13		0.000*
Khomas	-3.6	1.1	10.5	1	0.03(0.003,0.043)	0.001*
Kavango West	-0.2	0.3	0.3	1	0.9(0.5,1.6)	0.597
Zambezi	-1.4	0.3	22.3	1	0.2(0.1,1.0)	0.000*
Otjozondjupa	-0.8	0.5	2.7	1	0.5(0.2, 0.4)	0.102
Erongo	-1.1	0.6	3.8	1	0.4(0.1, 1.2)	0.051
Karas	-0.9	0.4	3.8	1	0.4(0.2,1.0)	0.051
Hardap	-18.9	13022.2	0.0	1	0.0(0.0, .)	0.999
Kunene	-0.4	0.4	1.4	1	0.7(0.3, 1.3)	0.230
Ohangwena	0.02	0.5	.002	1	1.02(0.4,2.7)	0.967
Omaheke	-.271	0.4	0.4	1	0.8(0.3, 1.7)	0.512
Oshikoto	-18.1	40192.9	0.0	1	0.0(0.0, .)	1.000
Oshana	-20.1	9665.9	0.0	1	0.0(0.0, .)	0.998
Omusati	-0.8	0.328	6.2	1	0.4(0.2, 0.8)	0.013*
Kavango East					1	1

Health facility			4.1	2		0.127
Hospital	-0.5	0.4	2.5	1	0.6(0.3,1.1)	0.112
PHC Clinic	0.01	0.3	0.001	1	1.01(0.6,1.6)	0.980
Health centre					1	
Sex						
Male	0.1	0.2	0.4	1	1.1(0.8,1.5)	0.541
Female					1	
Patient age (years)	0.026	0.005	25.5	1	1.02(1.01, 1.03)	0.000*
DOT provider			52.7	4		0.000*
Guardian	-3.4	0.5	46.2	1	0.03(0.01,0.09)	0.000*
Workplace	-22.6	7531.9	0.0	1	0.0(0.0,)	0.998
Health Facility	-2.8	0.5	30.4	1	0.1(0.02,0.2)	0.000*
Community H/worker	-3.0	0.8	16.1	1	0.05(0.01, 0.2)	0.000*
Other					1	
Sputum smear (month 2)			136.8	2		0.000*
Converted to smear -ve	-2.5	0.2	131.7	1	0.09(0.06,0.12)	0.000*
Remaining smear positive	-1.1	0.3	13.6	1	0.3(0.2,0.6)	0.000*
Defaulted+Transfered+Not available	16.1	40193.4	0.000	1	9351892.7	1.000
Exposure to IPT				1		0.135
Yes	0.6	0.4	2.2		1.8(0.8,3.8)	
No					1	
HIV status			31.5	2		0.000*
Negative	0.1	0.5	0.02	1	1.1(0.4,2.7)	0.898
Positive	1.9	0.5	13.5	1	7.2(2.5,20.9)	0.000*
Status not known					1	
Cotrimoxazole therapy						
No	0.8	0.3	6.1	1	2.2(1.2, 4.1)	0.013*
Yes					1	
ART co-medication						
Yes	0.04	0.2	0.03	1	1.03(0.7, 1.6)	0.850
No					1	
Constant	-16.9	40193.5	0.000	1	0.000	1.000

CPT = cotrimoxazole prophylaxis, IPT = isoniazid preventative therapy, ART = Isoniazid prophylactic therapy

6.5 Discussion

This study aimed to determine predictors of death among TB patients initiated on first line DOTS regimens in Namibia. In our sample, we found the death rate among TB patients ten times higher (i.e. 54% from the hospital-based study Table 1) and twice higher (i.e. 9.5% from the nation-wide ETR database study Table 3), than the national mortality rate

(i.e. 5%). [23,24] This is because we purposefully included patients with a death and cured outcome, and excluded the majority who are evaluated by treatment completion from the hospital study and those with poor outcomes in both studies.

Nonetheless, the annual TB report for 2016/2017 estimated 700 deaths from TB in Namibia, this is a high mortality rate (~7.9%) from one disease for a small population of 2.3 million people.[9] The findings of this study are comparable to studies done in Ethiopia, Thailand and Israel which found the case fatalities to range between 2.5%-41%, the highest being Israel.[25–27] However a similar study in Canada reported a low death rate (6.6%).[28] This variation is explained by different factors such as, the complexity of the disease among the patients and the HIV status of the patients.[6,29–31]For instance, our study had a higher number of HIV co-infected patients relative to other studies.[28,32] Indeed, half of deaths in the hospital-based study were co-infected with HIV coinfection, a risk factor for negative sputum smears and miss or under diagnosis. Lack of resources in Namibia could also have contributed to the higher death rate when compared to a high income country like Canada.[28,32]

Clinical characteristics were significantly associated with death outcomes, which included HIV status of patient, the type of TB, limited access to GeneXpert® in diagnosing TB and/or drug resistance, as well as use of sputum smear testing (Table 4). Indeed our study showed that a positive HIV status and limited access and use of GeneXpert® , higher age and cotriomoxazole prophylaxis as independent predictors of

death under the DOTS programme. Several studies in different parts of the world such as Cameroon, the United States, South Africa, and Ghana have found similar results where HIV was significantly associated with death outcome in TB patients. [33–36] Similar studies also found a significant association between extra pulmonary TB (EPTB) and death.[37] One study stated that patients with EPTB had three times more risk to die compared to those with Pulmonary TB.[38]

This study affirms that certain socio-demographic factors such as alcohol use, smoking and employment status of the patients are significantly associated with death outcome. Nonetheless, our study did not find any association between death outcome and gender and only age among the socio-demographic factors could independently account for the variances in death in the multivariate analysis (Table 4). Similarly, a study in Scotland showed no significant association between death of TB cases and socio-demographics of the patient such as gender, smoking, drug and alcohol abuse. [39] On the other hand, studies from Georgia and Egypt reported that females are more likely to have poor treatment outcome than male.[40]

The independent predictors associated with death outcomes in this study were a positive HIV status and non-access to the use of GeneXpert test in diagnosing TB. HIV negative patients were 80% less likely to die while on the DOTS programme compared to the HIV positive patients. These findings agree with results of a large South African TB programme showing a 5 times increased case fatality rate among TB/HIV positive patients

compared to HIV-negative patients. [41] Similarly, another study done in South Africa presented similar findings.[42] The authors in this study stated that HIV positive patients were more likely to have EPTB or have negative sputum smear TB, that are associated with increased mortality among TB patients [42], which was also observed in the bivariate, but not the multivariate analysis, in our study. Patients who were not diagnosed using GeneXpert test were also more likely to have a death outcome. WHO recommends the use of Xpert MTB/RIF (Mycobacterium and Rifampicin resistance) assay for rapid diagnosis of TB and detection of rifampicin resistance.[43]

In addition, the GeneXpert is a rapid and promising technique with good sensitivity (93%) and specificity (98.3%). [44] Perhaps the high case fatality amongst patients in this study may be explained by a missed diagnosis of drug-resistant strains and/or delayed access to TB care for patients.[44]

From the study we conclude that patients with a negative smear result (i.e. this is common among HIV patients and with EPTB) were more likely to die from TB. The main factors associated with death in this population were arguably clinical, that is HIV co-infection, diagnosis of extra pulmonary TB and having a negative smear pulmonary TB. The findings from this suggest that scale-up of the bacteriological and drug-resistance testing such as the rapid GeneXpert® may reduce the incidence of the death outcome.

Patient socio-demographic characteristics such as alcohol use, smoking and occupation were also significant factors associated with death, but not gender. This study recommends further strengthening of case management of patients with HIV-coinfection and those with negative smears. There is also a need to scale up rapid testing for TB and drug resistance in the community-based DOTS programme to aid the early diagnosis of TB and drug-resistance to enhance the quality of TB case-management at all levels of care. This will reduce reliance on the use of sputum smear microscopy, which has been found to be less sensitive among HIV-infected TB patients with low CD4 cell counts.

Limitations of the study

The results of this study should be interpreted with the following limitations. The study was retrospective that patient records and a data base with missing data on cases without the main outcome and/or variables. Even, then variable categories were analysed for distribution of missing data prior to inclusion in the model/ analysis. Nonetheless, the study provides a nation-wide baseline data on the predictors of death for future studies on the actual public health, clinical and biological determinants of death among TB patients. The study highlights that death is mainly due to clinical rather than sociodemographic characteristics or other factors.

Acknowledgments

We acknowledge the efforts of Ms. Anastasia Shekuhungama, my research assistant for facilitating the data collection and Sister Amutenya Faustina, the TB nurse of Khomas region for enabling the research team to access the patient files the process of data. We

also acknowledge the assistance given by the staff members of the Ministry of health and social services at TB facilities in Khomas region, particularly at Intermediate Hospital Katutura that supported the study.

Author contribution

DK played the leading role in conceptualizing, data collection, analysis and write up of the manuscript. AS assisted in conceptualization, data collection and management. RV, TR edited and appraised the paper during the various stages of publication. All authors permitted the submission of this paper to this journal.

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CHAPTER 7-8: TUBERCULOSIS DRUG PRODUCT - PHARMACOKINETIC AND PHARMACOVIGILANCE CONSIDERATIONSCONSIDERATION

CHAPTER 7: IMPACT OF HIV/AIDS ON PHARMACOKINETICS OF ANTI-TUBERCULOSIS MEDICINES

A meta-analysis of the impact of HIV/AIDS on serum levels of first line anti-tuberculosis drugs in the African population

Submitted to European Journal of Clinical Pharmacology (EJCP).

Published Verbeeck RK, Günther G, Kibuule D, Hunter C, Rennie TW. Optimizing treatment outcome of first-line anti-tuberculosis drugs: the role of therapeutic drug monitoring. European Journal of Clinical Pharmacology. 2016 Aug 1; 72(8):905-16.

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7.1 Abstract

Setting: HIV/AIDS is the main driver of the tuberculosis epidemic globally. The impact of HIV/AIDS on the pharmacokinetics of anti-tuberculosis drugs in Africa is inconclusive. *Objective:* The impact of HIV/AIDS on the maximum serum concentration (C_{max}) of first line anti-tuberculosis drugs in the African population was explored.

Methods: A systematic review and meta-analysis of maximum serum concentrations of rifampicin, isoniazid, pyrazinamide and ethambutol was conducted among TB patients with and without HIV co-infection in Africa. Fixed and/or random effects modelling using the Cochrane Revman® software version 5 was used to determine the pooled effect size (i.e. mean difference) in serum concentrations and heterogeneity among TB cases with/without HIV co-infection.

Results: Of the 26 pharmacokinetic studies, 11 (38.5%) met the Cochrane eligibility criteria for a meta-analysis. HIV/AIDS significantly lowered C_{max} of rifampicin -1.11µg/mL (95%CI: -2.18, -0.04, p=0.04, I^2=0%) and ethambutol -0.75 µg/mL (95%CI: -1.38, -0.13, p=0.02, I^2=0%) in the African population. The low levels among HIV co-infected patients were not significant for isoniazid (p=0.27) and pyrazinamide (p=0.14). The level of heterogeneity was low for rifampicin, ethambutol, pyrazinamide and isoniazid (I^2=0%).

Conclusions: HIV/TB co-infection increases the risk of low serum concentrations of rifampicin and ethambutol in the African population. Further efforts are needed to

optimize dosage regimens with rifampicin and ethambutol, and monitor C_{max} in HIV co-infected patients in Africa to improve treatment outcomes.

KEY WORDS: HIV/TB, FIRST-LINE DOTS, PHARMACOKINETICS,

7.2 Introduction

Tuberculosis (TB) and Human immune deficiency virus (HIV) infections are the major causes of morbidity and mortality in sub-Saharan Africa.[1,2] In 2015, there were 1.3 million new HIV infections and over 25.5 million people living with HIV (PLWHA) globally, 70% of these were from sub-Saharan Africa. [3–5] Of concern is that at least one-third of PLWHA globally are co-infected with TB [2] and TB remains the major cause of hospitalization and death among PLWHA. However in the sub-Saharan region, AIDS-related mortality reduced by 45% between 2005 and 2015.[3] This reduction has been attributed to increased access to antiretroviral therapy (ART) and Directly Observed Treatment-Short course (DOTS) programmes as well as the integration and strengthening HIV and TB health care services particularly in primary health care.[6–8]

Nonetheless, poor TB treatment outcomes (i.e. treatment failure, death, treatment default and drug resistance) remain a major barrier to eliminating TB in this region.[9] For instance, most sub-Saharan countries have not achieved the 90% global treatment coverage and treatment success rate (TSR) targets for tuberculosis.[10] In contrast, these targets reached by most West-European and North-American countries.[11–13] Furthermore, five countries in sub-Sahara Africa (i.e. Swaziland, Lesotho, South Africa and Namibia), are high TB

and HIV burden settings in the world.[5,14] Several studies have attributed poor TB treatment outcomes to sub-therapeutic serum levels of anti-tuberculosis medicines, especially among patients co-infected with HIV among other factors. [15–19] For instance, studies have shown plasma levels of rifampicin to be below target concentrations (i.e. <8µg/mL) in up to 75% of patients.[20–23] On the other hand, some studies show no significant relationship between HIV coinfection and serum levels of first-line TB medication,[20,24–27] and/or tuberculosis treatment outcomes.[28]

The interplay between TB/HIV disease severity and other patient factors such as age[29,30], comorbidities[31], sex and pharmacogenetics[32–34] has not been systematically reviewed in the sub-Saharan population. Furthermore, there are conflicting reports on the relationship between sub-optimal serum levels of first-line anti-tuberculosis treatment with treatment outcomes.[35] Indeed, knowledge on the effect of HIV/AIDS on pharmacokinetics of TB medication would provide direction on the appropriate dosage adjustments and improve treatment outcomes.

Consequently, the aim of this study was to systematically evaluate published articles to determine the magnitude of the impact of HIV/TB co-infection on the C_{max} of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) in the African population in order to provide guidance for rational case management of TB patients at risk of poor serum levels and/or treatment outcomes.

7.3 Methods

7.3.1 Design, search strategy and inclusion criteria

A systematic review of studies published in English between January 2000 and May 2018, (i.e. a period during which community-based DOTS was implemented worldwide) that had assessed the pharmacokinetics and/or serum concentrations of first line anti-tuberculosis drugs among TB patients with or without HIV co-infection in Africa was conducted. The search strategy detailed in **Appendix C** included three key search terms that is pharmacokinetics, first line anti-tuberculosis drugs and the African countries specific search term. Boolean operators such as AND, OR and NOT, with extensions * and wt., were used alongside the synonyms (e.g. serum levels, plasma levels, serum concentrations, plasma concentrations, rifampicin, rifampin, pyrazinamide, isoniazid, ethambutol etc.) for the key terms to focus the search.

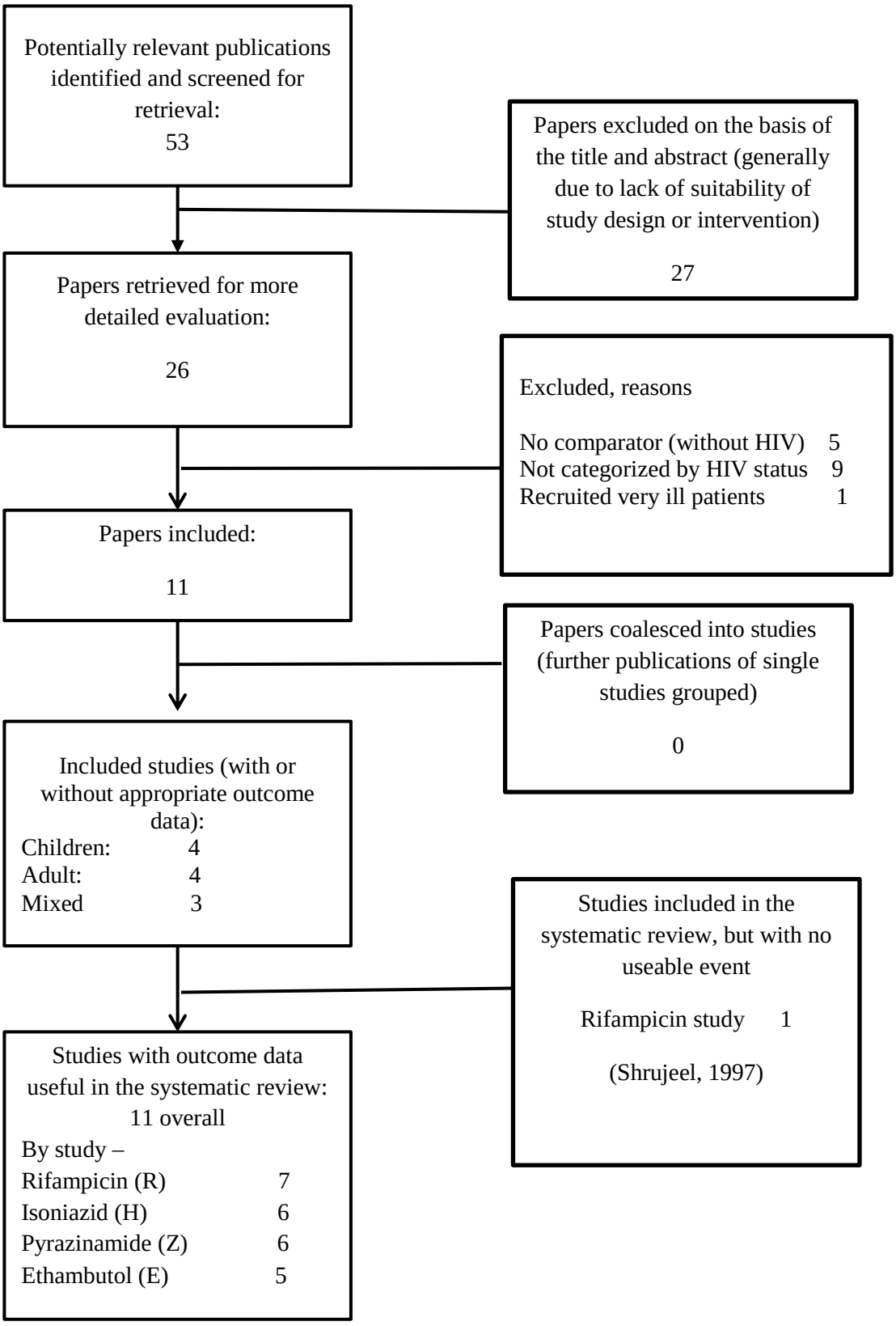
The search strategy employed was (pharmacokinetics) AND (rifampicin OR isoniazid OR pyrazinamide OR ethambutol) AND (tuberculosis) AND (the African countries specific search term, **Appendix C**). The search strategy was applied in search engines or data bases that included Mendeley, PubMed, EMBASE, Google scholar, Cinahl, Cochrane library, Scopus, African Journals Online and the reference lists of retrieved articles were also reviewed to identify other studies in gray literature. We also contacted individual authors for original articles and findings for papers we could not access online. The papers that were relevant to the study objectives were identified by three reviewers (DK, RV and SM) and their abstracts and full papers reviewed for inclusion. The reviewers independently included studies based on the eligibility criteria and methodological quality recommended

by Cochrane review.[36,37] The search returned 26 articles and 10 met the review criteria and were included in the meta-analysis (Table 1).

Only studies with prospective, randomized control trials (RCT), and cohort design that exclusively reported on the Cmax of any of the first-line TB medication, RHEZ in the African population were included in the final data sample for analysis. The target comparator populations were TB patients with/without HIV co-infection.

The intervention was TB treatment regimen with first line anti-tuberculosis, i.e. rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E). The main outcome measure in the study meta-analysis was the mean plasma concentration (C_{max}) and/or proportion (percent, %) of patients with sub-optimal C_{max} for the individual the first line medicines among patient with/without HIV co-infection. In this study sub-optimal C_{max} were <8 µg/mL for rifampicin, <3 µg/mL for isoniazid, <35 µg/mL for pyrazinamide, and < 2 µg/mL for ethambutol as recommended by the World Health Organisation. [9,50] However, though there is conflicting relationship on the plasma sub-optimal concentrations and treatment outcomes, with some studies reporting poor outcomes and others no effect. [23,38–41] We excluded studies with only one arm of patients (i.e. either HIV/TB co-infected or TB patients without HIV) and studies that did not report C_{max} for the two groups.

Figure 1. Flow diagram of the systematic review (Quorum statement flow diagram)



7.3.2 Statistical analysis

We aimed to test the hypothesis of a zero-effect size (i.e. Mean difference and/or odds ratio) in C_{max} of first-line antituberculosis medicines among TB patients with/without HIV co-infection in the African population. All statistical analyses were performed in Revman® (version 5.3) and RStudio (version 3.3.3) software. Data on the main event, that is the number of patients with C_{max} below target levels and/or the mean C_{max} ± standard deviation (SD) for each first-line anti-tuberculosis drug were compared among TB patients with HIV coinfection ("intervention group") and TB patients without HIV infection ("control group"). These were extracted from the articles and entered into Revman (version 5.3) software for quantitative analysis.

The pooled effect size of the impact of HIV on the C_{max} was estimated using odds ratios (OR) for studies that reported C_{max} outcomes as a categorical outcome and mean difference (MD) for continuous outcome as a 95% confidence interval using either fixed/random effect modelling suggested. In addition, the Cochran Q-test was used to test the null hypothesis of no significant heterogeneity across the studies included in the meta-analysis for each first-line anti-tuberculosis drug. The percentage of variation (i.e. I^2) in the measures of association between HIV coinfection and C_{max} was also determined, this ranges between 0% (no heterogeneity) and 100% (high heterogeneity). The level of significance for the analysis was set at a Type I error (α) of 0.05 for a 95% confidence interval.

7.3.3 Ethics

Research and ethics committees of the Ministry of Health and Social Services (MoHSS17/3/3/November 2015) and University of Namibia (SOM/114/2016) approved the study. The need for written informed patient consent was waived as the study used published secondary population level data.

7.4 Results

The search strategy identified 26 studies [13, 16, 25-41] that investigated the C_{max} of first line anti-tuberculosis medicines among TB patients with/without HIV co-infection in African countries. Eleven (11) prospective and/or randomized trials were eligible for inclusion in the meta-analysis. [13, 16, 25-31] Four of these studies investigated the pharmacokinetics of first line anti-tuberculosis medication, i.e. RHZE among children, 3 studies had mixed populations (i.e. recruited children and adult patients) and 4 were among adult patients (> 18 years).

7.4.1 Studies included and excluded in the meta-analysis and review

Table 1: studies included and excluded in the meta-analysis and review

Study ID	**Study title**	**Eligibility**	**Setting**/Design	Reason for inclusion /exclusion
Yang, 2018[42]	Evaluation of the Adequacy of the 2010 Revised World Health Organization Recommended Dosages of the First-line Antituberculosis Drugs for Children	Included	Ghana Prospective cohort Children (n=100) Sampling: 4 weeks treatment AUC0-8h	A prospective study that assessed Cmax of RHEZ among children with/without HIV based on WHO weight band dosing
Antwi, 2017[43]	Pharmacokinetics of the first-line anti-tuberculosis drugs in Ghanaian children with tuberculosis with or without HIV co-infection	Included	Ghana Clinical Trial Children (n=113) Sampling: 4 weeks AUC0-8h	A clinical trial that assessed Cmax in both patients with/without HIV co-infection on

				WHO weight band dosing
Kwara, 2016[44]	Pharmacokinetics of first-line antituberculosis drugs using WHO revised dosage in children with tuberculosis with and without HIV coinfection	Included	Ghana Clinical Trial Children (n=62) Sampling: 4 weeks AUC0-8h	A prospective observational study that assessed Cmax in children on the WHO weight band dosing for RHEZ
Graham,2006[20,27]	Low levels of pyrazinamide and Ethambutol in children with tuberculosis and impact of age, nutritional status, and human immunodeficiency virus infection	Included	Malawi Cross-sectional Prospective cohort Children (n=27) Sampling: intensive phase AUC0-48h	A prospective cohort study that assessed Cmax for E and Z among children on WHO weight band dosing
Rockwood, 2016[45]	HIV-1 Coinfection Does Not Reduce Exposure to Rifampin, Isoniazid, and Pyrazinamide in South African Tuberculosis Outpatients	Included	South Africa Prospective observation Adults (n=100) Sampling: 7-8 weeks AUC0-8h	A prospective study that assessed the Cmax of RHZ among adult patients based on WHO weigh band dosing
Chedeya, 2009[23]	Isoniazid, rifampin, Ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana.	Included	Botswana Prospective cohort Adults (n=255) Sampling: 14 days AUC0-6h	A prospective cohort study that assessed Cmax for RHEZ based on the WHO weight band dosing
Shrurjeel, 1997	Pharmacokinetics od antimycobacterial Drugs in patients with tuberculosis, AIDS, and Diarrhea	Included	Kenya, Nairobi Prospective cohort Adults (n=29) Sampling: ≥7 days AUC0-12h	A cross-sectional study that assessed the Cmax of RHZ among adult patients based on WHO weigh band dosing
Tappero 2005[46]	Serum concentrations of antimycobacterial drugs in patients with pulmonary tuberculosis in Botswana	Included	Botswana Prospective cohort Adults (n=91) Sampling: > 7 days AUC0-6h	A prospective cohort study that assessed Cmax for four RHEZ on WHO weight band dosing
Djadji, 2015[47]	Pharmacokinetics of isoniazid in 30 tuberculosis patients in Abidjan, Côte d'Ivoire	Included	Ivory coast Prospective analytical study cohort Adults (n=30) Sampling: 1 day AUC0-12h	A prospective study that assessed Cmax of isoniazid West African population.
Choudhri,1997[25]	Pharmacokinetics of antimycobacterial drugs in patients with tuberculosis, AIDS, and diarrhea	Included	Kenya Prospective analytical study cohort Adults (n=30) Sampling: day 13 and 14 AUC0-12h	Assessed Cmax of RHZ using weight band dosing

Schaaf, 2009[48]	Rifampin pharmacokinetics in children, with and without human immunodeficiency virus infection, hospitalized for the management of severe forms of tuberculosis	Included	South Africa Prospective cohort Adults (n=54) Sampling: 1 and 4 months AUC0-6h	A prospective cohort study assessed Cmax for R based on weight band dosing after1 and 4 months after treatment
Bhatt,2014[49]	Pharmacokinetics of rifampin and isoniazid in tuberculosis-HIV co-infected patients receiving nevirapine-or efavirenz-based antiretroviral treatment	Excluded	Mozambique	Study done only in HIV/TB patients. No comparator group of patients without HIV
Chirehwa, 2014[50]	Population pharmacokinetics of pyrazinamide among HIV/TB co-infected patients at different levels of immunosuppression in South Africa	Excluded	South Africa/ Prospective	Study done only in HIV/TB patients. No comparator group of patients without HIV
McIlleron, 2012[51]	Reduced Antituberculosis Drug Concentrations in HIV-Infected Patients Who Are Men or Have Low Weight: Implications for International Dosing Guidelines	Excluded	South Africa Prospective cohort Adults (n=60) Sampling: 1month AUC0-12h, weekly – i.e. on day 1,8, 15 and 29	A prospective cohort study that assessed Cmax for RHEZ based on the WHO weight band dosing at every after each week. Included on HIV patients
Denti, 2015[39]	Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in Newly Diagnosed Pulmonary TB Patients in Tanzania	Excluded	Tanzania/ Clinical Trial	Study did not categorized pharmacokinetics for TB patients by HIV status
Hiruy, 2014 [52]	Subtherapeutic concentrations of first-line anti-TB drugs in South African children treated according to current guidelines: The PHATISA study	Excluded	South Africa/ Prospective observational	Study did not categorized pharmacokinetics for TB patients by HIV status
Jonsson,2011[53]	Population Pharmacokinetics of Ethambutol in South African Tuberculosis Patients	Excluded	South Africa/ Population PK	Study did not report on Pharmacokinetics by HIV status
McIlleron, 2006[54]	Determinants of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Pharmacokinetics in a Cohort of Tuberculosis Patients	Excluded	South Africa/ Prospective observational	Study did not dichotomize serum levels by HIV status

Mlotha, 2015[27]	Pharmacokinetics of anti-TB drugs in Malawian children: reconsidering the role of ethambutol	Excluded	Malawi	Study did not dichotomize serum levels by HIV status
Mtabho, 2012[55]	Plasma levels of tuberculosis drugs in TB patients in northern Tanzania	Excluded	Tanzania/ observational pharmacokinetic	Study did not dichotomize serum levels by HIV status
Oosterhout, 2015[26]	Pharmacokinetics of antituberculosis drugs in HIV-positive and HIV-negative adults in Malawi	Excluded	Malawi/ AUC0-24 h	Study did not report on the serum levels by HIV status. The data is not available
Pasipanodya[15]	Serum Drug Concentrations Predictive of Pulmonary Tuberculosis Outcomes	Excluded		Study did not dichotomize serum levels by HIV status
Salieri, 2012 [56]	Systemic exposure to rifampicin in patients with tuberculosis and advanced HIV disease during highly active antiretroviral therapy in Burkina Faso	Excluded	Burkina Faso/ Prospective, longitudinal	No comparator of patients without HIV
Sloan, 2014[57]	Pharmacokinetic Variability in TB Therapy: Associations With HIV and Effect On Outcome	Excluded	Southern Africa/ Cross-sectional	No comparator of patients without HIV
Sekaggya-Wiltshire, 2014[58]	Low isoniazid and rifampicin concentrations in TB/HIV co-infected patients in Uganda	Excluded	Uganda/ Cmax:1,2,4h	No comparator of patients without HIV
Tostmann, 2013[59]	Pharmacokinetics of first-line tuberculosis drugs in Tanzanian patients	Excluded	Tanzania	Study did not report dichotomize serum levels by HIV status
Koegelenberg, 2013[60]	The pharmacokinetics of enteral antituberculosis drugs in patients requiring intensive care.	Excluded	South Africa	Study recruited very ill patients which is not routine for DOTS

7.4.2 Effect of HIV co-infection on mean C_{max} of rifampicin

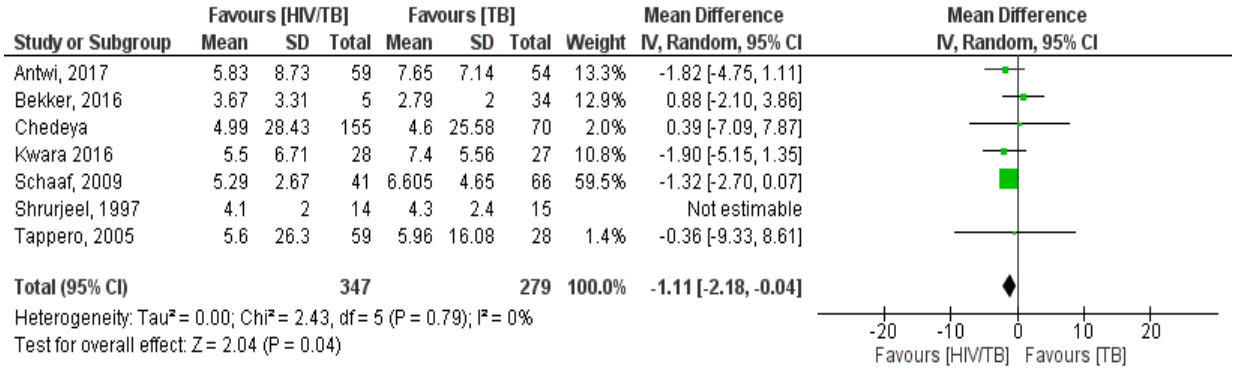


Figure 2: Effect of HIV co-infection on mean C_{max} of rifampicin

Of the six (6) studies included in the meta-analysis for rifampicin, all showed no significant difference in the mean C_{max} among TB patients with/without HIV co-infection (Figure 1a, i.e. mean differences crosses the null). However, most studies (4 out of 5, 80%) report a lower mean C_{max} among patients with HIV coinfection. The overall effect of the pooled studies showed a significantly lower C_{max} of rifampicin among patients with HIV (p=0.04) with a mean difference of -1.11 µg/mL compared to TB patients without HIV (Figure 2). The Cochran Q test did not show significant heterogeneity in the studies (p>0.05) and I^2=0%. Similarly, the funnel plot showed no publication bias (i.e. symmetrical shape) in the inclusion of studies in the meta-analysis for rifampicin (Figure 3). On contrary, the percentage of patients with sub-therapeutic rifampicin concentrations (i.e. Cmax < 8 µg/mL), was 30% more among cases without compared to those with HIV coinfection, this was however not statistically significant (p>0.05).

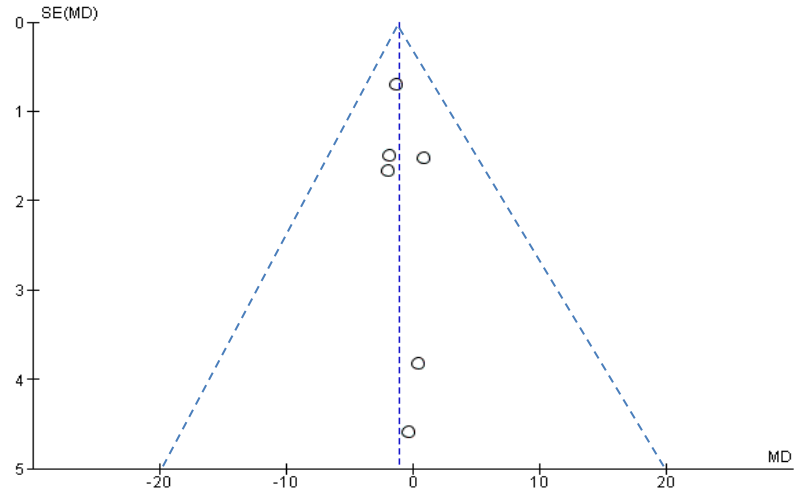


Figure 3: Funnel plot for rifampicin studies included in meta-analysis

7.4.3 Effect of HIV co-infection on mean C_{max} of isoniazid

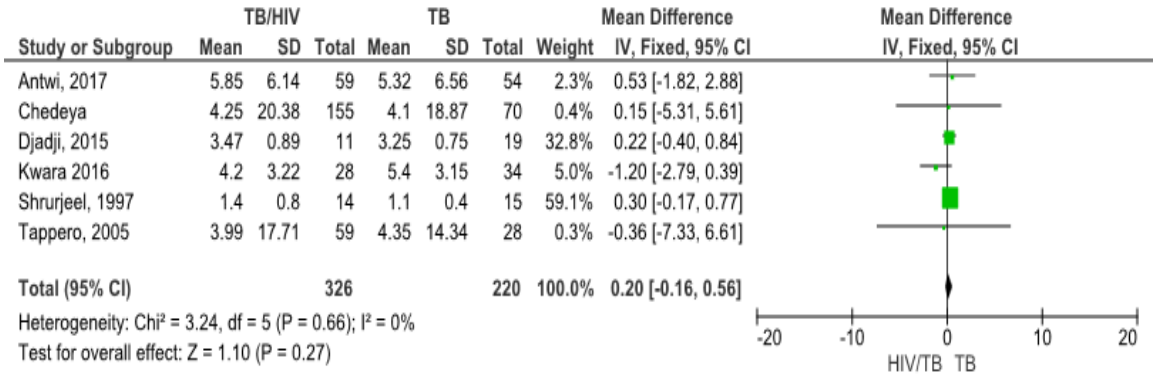


Figure 4: Effect of HIV/TB co-infection on mean C_{max} of isoniazid

Of the six studies (6) in the meta-analysis for isoniazid (H), all showed no difference in the mean C_{max} (i.e. the 95% CI of individual studies crosses the zero difference point) between patients with or without HIV coinfection. Similarly, the pooled mean difference in C_{max} for isoniazid was not significantly different among patients with or without HIV

coinfection (p>0.27). There was no heterogeneity among the studies (Cochran's Q test > 0.05, and I^2=0%). Moreover, the mean C_{max} for isoniazid was 0.2 µg/mL lower among TB patients with HIV co-infection than those without (Figure 4). The funnel plot was symmetrical indicating no publication bias in the inclusion of studies in the meta-analysis (Figure 5).

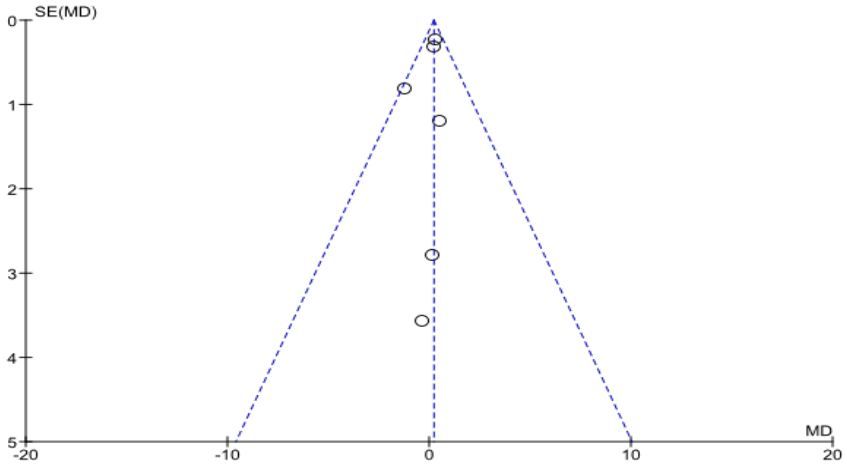


Figure 5: Funnel plot for isoniazid studies in the meta-analysis

7.4.4 Effect of HIV co-infection on mean C_{max} of ethambutol

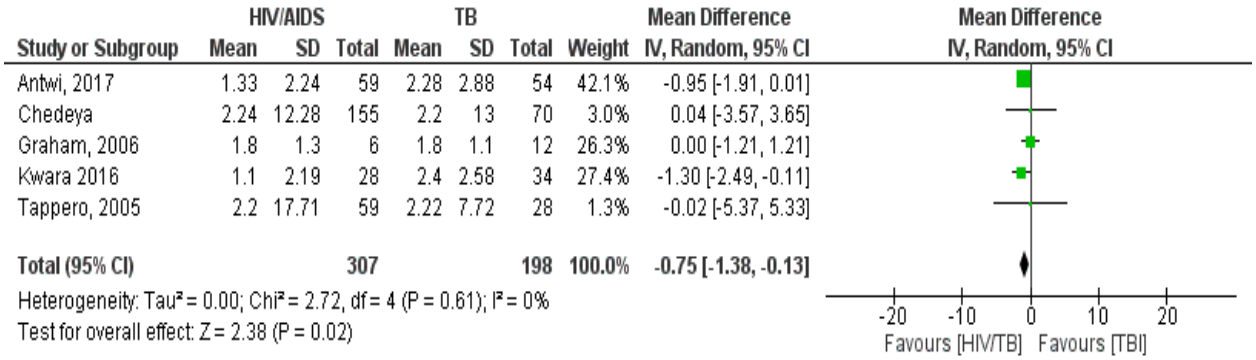


Figure 6: Effect of HIV/TB co-infection on mean C_{max} of ethambutol

Of the five studies included in the meta-analysis for ethambutol, all showed no significant difference in the mean C_{max} among patients with or without HIV coinfection, (i.e. the 95% CI for the five studies crosses the zero, no difference point). However, one out of the five studies appeared to show higher mean C_{max} among patients without HIV coinfection. Nevertheless, the pooled effect model showed that the mean C_{max} of ethambutol significantly lower among TB patients with HIV coinfection (p=0.02) than those without (Figure 6). The meta-analysis showed no heterogeneity among the studies on ethambutol. Similarly, the funnel plot was symmetrical indicating no publication bias in the inclusion of studies in the meta-analysis for ethambutol (Figure 7).

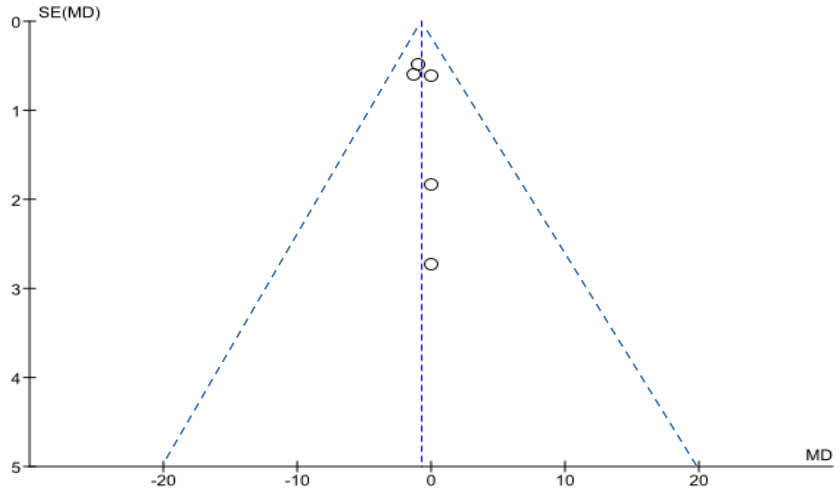


Figure 7: Funnel plot for ethambutol studies in the meta-analysis

7.4.5 Effect of HIV co-infection on mean C_{max} of pyrazinamide

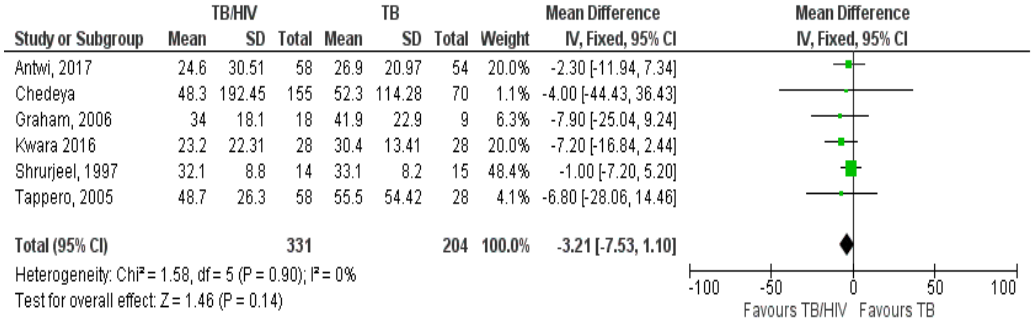


Figure 8: Effect of HIV/TB co-infection on mean C_{max} of pyrazinamide

Lastly, of the six studies included in the pyrazinamide meta-analysis, none had a significant difference in the mean C_{max} among patients with or without HIV co-infection. The overall effect of HIV infection on the mean C_{max} of pyrazinamide was not significant ($p>0.90$) (Figure 8). There was no heterogeneity between the individual studies on pyrazinamide. The funnel plot was symmetrical indicating no publication bias in the inclusion of studies in the meta-analysis for pyrazinamide (Figure 9).

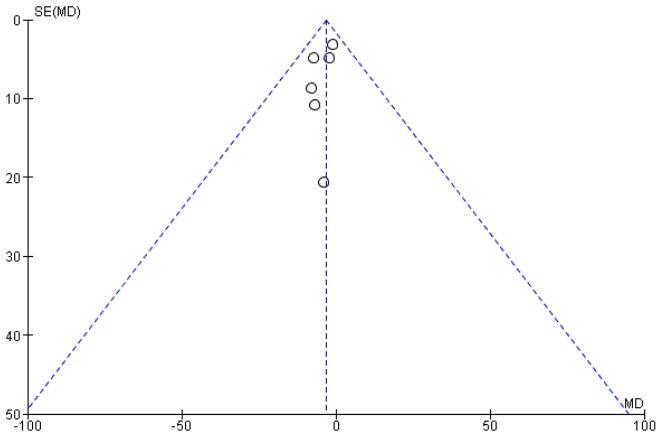


Figure 9: Funnel plot for pyrazinamide studies in the meta-analysis

7.5 Discussion

Whilst we accepted that HIV/AIDS impacts negatively on pharmacokinetics of first-line TB medication, the magnitude of this effect has not been systematically studied in the African population, where the HIV/TB burden is greatest. Previous studies have described genetic polymorphism (i.e. variations in enzymes and/or transporters involved in the disposition of isoniazid and rifampicin) as a risk factor for sub-therapeutic levels of TB medication.[32,44,59] Among other patient level determinants of sub-therapeutic plasma concentrations of anti-tuberculosis medications is HIV infection, gastrointestinal tract disorders, high body weight, male gender or diabetes mellitus. [61–63]

McIlleron *et al.*, showed that TB cases with HIV co-infection had a 39% and 27% reduction in plasma concentrations of rifampicin and ethambutol respectively. [51,54] The impact of weight on serum levels of anti-TB drugs is particularly important, when standard doses (i.e. mg/kg) are used for first-line drugs, where patients with low weight are likely to have lower levels. McIlleron *et al.,* and other studies also identify dosage formulation, the female gender, old age, previous exposure to anti-tuberculosis treatment and dose determination (i.e. weight-band dosing) as risk factors for sub-therapeutic plasma concentrations of some or all four first line TB drugs.[51,54,64,65]

Based on current evidence on the African population, we found that although TB patients with HIV co-infection had lower C_{max} levels for all first-line medicines this was only statistically significant for rifampicin and ethambutol (Figure 1 and 3). Thus, low C_{max} levels are common among TB patients with HIV co-infection.[66,67] Perhaps, the low C_{max} across all first-line anti-tuberculosis medicines may be attributed drug interactions with

HIV disease and/or co-medication (i.e. ART medication including ARVs and medications for opportunistic infections).[7,68] Our finding for isoniazid and pyrazinamide affirm other studies that showed no difference in the mean C_{max} among TB patients with/without TB co-infection.[1-4]

However our findings for rifampicin and ethambutol agree with several studies that report significantly low levels among patients with TB/HIV co-infection.[44,46,51,54,69] Nonetheless the findings from the meta-analysis and other studies suggest that plasma levels for rifampicin and/or ethambutol[70] should be monitored and/or higher doses should be administered among HIV co-infected patients at risk of poor treatment outcomes.

A plausible explanation of lower mean C_{max} plasma levels among TB/HIV co-infected TB patients is a complex interplay of several covariates in addition to HIV that lead inter/intra-individual variability in pharmacogenetics, gender, age of the patient as well as nutritional status.[17,20,71,72] For instance, genetic polymorphism of isoniazid and rifampicin is widely reported in the African population.[44,51,59,73] The two medicines (i.e. rifampicin and ethambutol) are a critical component of the first-line anti-TB regimens used globally, particularly in areas of high TB resistance such as Namibia. Thus, a low systemic exposure to rifampicin is associated with the development of secondary resistance that is drug resistant TB (i.e. MDR-TB and XDR-TB) as well as poor treatment outcomes. The wide variability in prevalence (%) of low rifampicin levels across the studies compared to the plasma concentrations may have led to non-significance of the effect size of HIV on rifampicin levels which may be due to differences in methodologies used in the different studies.

The study conclude that TB/HIV co-infected patients are at increased risk of sub-therapeutic serum concentrations of rifampicin and ethambutol. There is no difference in the occurrence of low serum levels of pyrazinamide and isoniazid among patients with or without HIV co-infection. The pharmacokinetics of rifampicin and isoniazid are more likely to be also influenced by intra/inter-individual variability such as genetic polymorphism[18] and drug-drug/food interaction[74,75]. Moreover, the absorption of pyrazinamide has also been shown to be affected by food.[20,76] This calls for individualized dosage adjustments of R and E , and other first line anti-TB drugs in patients co-infected with HIV.[70,77]

The findings from this systematic review should be interpreted with limitations. Most importantly, there are limited randomized control trials (RCTs) comparing pharmacokinetics of TB patients across countries and populations in Africa. In addition, some studies included in the systematic review were conducted on a limited number of patients and in mixed populations or among children whose absolute drug exposure are found to be low even after the revised WHO 2010 guideline change. Some studies were excluded because they did not report on HIV uninfected patients, or written in English or the search could not pick out studies published in languages other than English. There was a wide variability in the methods and/or formulation used in the different studies. Nonetheless, the studies showed no heterogeneity and the findings from this meta-analysis provide preliminary information on the impact of HIV/TB co-infection on PK of all the first line anti-tuberculosis drugs across African countries.

Acknowledgements

The authors wish to acknowledge the assistance rendered by the staff at the University of Namibia, Health Sciences Campus Library in particular Ms. M. Shatona as well as the authors of various manuscripts who provided additional information on their papers when requested particularly Prof. Antwi and Prof. Van Oosterhout.

The authors declare no conflict of interest. This study did not receive any specific grant from any funding agency in the public, commercial or non-profit sectors.

Author contribution

DK played the leading role in conceptualizing, data collection, analysis and write up of the manuscript. SM and RV assisted in search and appraisal of the articles. RV, EE, TR edited and appraised the paper during the various stages of publication. All authors permitted the submission of this paper to this journal.

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CHAPTER 8: BURDEN OF DOT RELATED ADVERSE DRUG REACTIONS

The burden of adverse drug reactions among patients on first line dot regimens in Namibia

Submitted to Drug Safety and Pharmacovigilage Enliven

Submitted to *5th Medicine Utilization Research in Africa (MURIA) Symposium in collaboration with International Society for Pharmacoepidemiology (ISPE), July 2019 North West University, South Africa.*

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8.1 Abstract

Background: Namibia achieved universal coverage of Directly Observed Treatment-Short course (DOTS) for tuberculosis in 2015. However, the safety of first line DOTS regimens is unknown in Namibia. This negatively affects treatment adherence and success rates.

Objective: The burden and grades of adverse reactions associated with first line DOTS regimens in Namibia were explored.

Methods: A hospital-based cross-sectional survey at a regional referral TB hospital, Intermediate Hospital Katutura (IHK) was conducted from 29 June to 29 August 2016. The main outcome measure were the incidence, grades and factors associated with adverse effects among TB cases on first line DOTS regimens. Data on socio-demographic and clinical characteristics were abstracted from the patient treatment records, and through patient interviews. Descriptive and bivariate analysis were used to determine the incidence and grades, and factors associated with adverse drug reactions using SPSS software v 22.

Results: Out of 100 patients recruited in the study, 69% experienced at least one adverse drug reaction while on first line DOTS regimens. Type-A (i.e. predictable adverse drug reactions) were the most common and ranged from 9% to 69%. The rate of Type-B adverse drug reactions (i.e. Unpredictable reactions such as allergy and hypersensitivity reactions) was 26%. The most common Type-A ADR were gastrointestinal disturbances (n=69/100, i.e. diarrhoea, nausea and/or vomiting), musculoskeletal (n=28/100, i.e. joint and muscle pains) and neurological (i.e. disturbed visual acuity, 10% and peripheral neuropathy, 9%). The frequency of adverse reactions was higher among TB patients with;

HIV co-infection than those without (78.5%, *p*=0.003), low baseline body weight (*p*=0.002) and being on concomitant therapy with ART (76.2%, *p*=0.012) or cotrimoxazole (78%, *p*=0.005). The incidence of moderate to severe grade adverse reactions was less than 5%.

Conclusion: There is a high burden of adverse reactions associated with first line DOT regimens. There is need to incorporate active pharmacovigilance reporting in DOTS programme particularly among patients with HIV coinfection, underweight and antiretroviral treatment.

KEY WORDS: ADVERSE DRUG REACTIONS, DOTS, TUBERCULOSIS

8.2 Introduction

Tuberculosis (TB) a curable disease, is the second most common cause of death from an infectious disease globally.[1,2] The World Health Organisation (WHO) projects that a further 35 million deaths will occur if TB is not abated by 2035.[3,4] The death rates are higher among TB cases with HIV co-infection.[5–7] It is not surprising that 98% of the deaths are from the developing countries such as Namibia with the highest burden TB and Human Immunodeficiency Virus (HIV) infections in the world.[8–10] In Namibia, TB is among three most frequent causes of hospitalizations and deaths.[11]

On the other hand, the implementation of the Directly Observed Treatment Short course (DOTS) strategy has improved tuberculosis treatment success across countries.[9,12,13] For

instance, Namibia achieved universal access to high quality DOTS services in the community.[14,15] In the community-based DOTS (CB-DOTS) approach, the observation of administration of TB treatment is done by DOT supporters (i.e. relatives and family, and work supervisors and community health workers.[14] Consequently, since the implementation of the CB-DOTS programme in Namibia in 2005, the number of patients completing treatment TB treatment has increased and has improved the treatment success rates from 64% in 2004 to over 85% in 2015.[11,16–18] However, poor treatment outcomes such as death, loss to follow up and treatment failure remain common under the DOTS programme in Namibia and in most developing countries.[11,19] The poor treatment outcomes are partly attributed to non-adherence to TB treatment due to mild and/or life-threatening adverse effects.[5,20–22]

There is growing evidence that adverse reactions (ADRs) associated with TB-medication are a risk factor to adherence to treatment and poor outcomes such as death and loss to folow-up.[5,23–26] Moreover, severe adverse reactions such as drug-induced hepatotoxicity[27,28] cutaneous reactions and neuropathies often lead to interruption of treatment with first line treatments. A study in Nepal reports that ADRs account for 5 % of all hospital admissions and caused death in 0.1% of TB cases .[29,30] Moreover, a survey in Namibia by Sagwa *et al.* (2012) on ADRs among TB patients on second line-DOTS regimens found the occurrence of tinnitus at 45% versus lower rates reported in literature (5.1% - 24%) and for hearing loss (25% vs range: 6.7% - 33%).[23] As a result, adverse drug reactions associated with DOTS regimens cause significant morbidity and impede treatment success.[23,31–37] Little is known about the occurrence of ADRs among patients on

first line regimens under the DOTS programme in Namibia, who form the significant proportion of patients on TB treatment.

The risk factors ADRs for first line DOTS treatment have been contested across studies; which include liver disease, HIV or hepatitis C coinfections, drug regimen, and intensive phase, alcohol intake, female sex, ethnicity, drug abuse and nutritional status.[33,38–41] Consequently, the aim of the study was to assess the occurrence of DOTS associated ADRs in Namibia to provide guidance on case management.

8.3 Methods

8.3.1 Study design and subjects

Two studies were conducted, a systematic review and a hospital-based crossectional analytical study to compare the global and Namibian burden (incidence and grades) of ADR among patients on first-line DOT regimens. The first line regimens are 2HRZE/4HRE and 1RHZES/2RHZE/5RHE (RHEZ, i.e. rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin) new and retreatment TB cases.[42,43] Firstly, we performed a systematic review of published literature on the burden and risk factors of ADR associated with first line DOTS regimens using the Cochrane® methods for a systematic review. The hospital study applied methodologies of crossectional analytical design and targeted all TB patients (i.e. ambulatory and hospitalized) receiving first line DOTS regimens at the TB hospital of Intermediate Hospital Katutura in Windhoek.

8.3.2 Data collection

8.3.2.1 Data for the systematic review

Articles on the rate and risk factors for ADRs associated with first line TB regimens published from 1998 to 2018 were identified using a search strategy and were subsequent abstracted for descriptive and thematic analysis. The search terms were "adverse drug reactions" and "first line antituberculosis treatment" with corresponding synonyms alongside Boolean operators were entered in search engines including PubMed, Medline and google scholar, Scopus and Mendeley. Only studies that reported the rate (i.e. prevalence or incidence) and risk factors for ADR among patients on first line DOTS regimens were included in the study. The abstracts and full articles were also assessed for quality based on the Cochrane criteria for a systematic review. Two researchers independently selected the articles to be included in the review based on the Cochrane criteria, and where there were differences in the selection, a second opinion was sought from the supervisors of the study.

8.3.2.2 Data collection for the hospital-based study

Data on the occurrence and type of ADRs as well as patient socio-demographic, clinical and treatment characteristics were collected by patient interviews and abstraction (Supplement) from the TB treatment files over a two-month period, 29 June to 29 August 2016. All patients who were hospitalized at the time of study were eligible for the study. All patients had to be on TB treatment for at least two months to be eligible for the study. The socio-demographic, clinical and treatment factors were assessed.

Patients were sequentially selected using a set of random numbers generated by a computer based on the attendance register and their treatment records were subsequently reviewed and interviewed for ADRs and other clinical and laboratory covariates. On the day of data collection, after receiving written informed consent from the patients, data on patient demographics, treatment and clinical covariates were abstracted from patient TB treatment cards and/or registers. The causality and grades of the adverse drug reactions associated with first line ADR was determined based on the Narajo[44] and WHO toxicity scoring scale[45] respectively.

8.3.3 Statistical analysis

The data on ADR were verified with the physician on duty and the data were subsequently entered into Epi-data v3.1 software for management (i.e. check for errors and outliers in the data) and then exported to SPSS v 22 for descriptive quantitative analysis. The outcome measures were the rate of occurrence, types, grades and factors associated with adverse drug reactions. The rate of ADRs associated with first line DOT regimens was determined using descriptive statistics (i.e. percent, %) and the associated factors by Chi-square test. The practical significance of the association between a patient and/or clinical covariate was determined using a Cramer's V statistic (i.e. with Cramer's $V \geq 0.5$ defined as practical significance). For all statistical analysis, the level of significance (α) was set at $p = 0.05$ for a 95% confidence interval. The analysis for the systematic review was done by descriptive and thematic analysis.

8.3.4 Ethics

Ethical considerations for this study were met by the following: permission to conduct the research was granted by the University of Namibia (UNAM, SOM/114/2016) and Ministry of Health and Social services (MoHSS17/3/3/November 2015). Confidentiality of the patients' information was kept by use of codes in place of patient identifiers and no direct involvement of third parties in handling of the data and records were kept in a locked cupboard in a lockable office, on a security-controlled campus at the School of Pharmacy, University of Namibia.

8.5 Results

8.5.1 Systematic review of ADR associated with first line DOTS regimens

8.5.1.1 Prevalence of ADRs associated with first line DOTS regimens

The search strategy for publications on adverse drug reactions from 1998 - 2018 returned 72 articles, 26 of these met the inclusion criteria (Table 5). Of the 26 studies , 12 (46.2) described the prevalence[34,36,37,39,46–53] and 2 studies described the incidence rate[47,54]of ADRs of first line DOTS regimens across all patients on treatment for active TB. The mean prevalence for at least one ADR was 50.1±21.9 range (7.2%-83.3%). Among these, 2 studies estimated the risk of adverse effects to be greater among HIV (Average = 41.2%) compared to patients without HIV coinfection (average = 6.8%).

The prevalence of mild adverse effects was 72.5±20.6%, range (46.7%-93.3%) and for severe adverse drug reactions 18.1±16.0%, range: (0%-39.9%). The prevalence of ADRs related to gastrointestinal 28.1%, range: (2.5%-87.1%), cutaneous 12.0% range: (2%-

43.5%), hepatotoxicity, 35.2% range (2.6%-86.9%) and neurological 8.8% (0.1, 14.3%), musculoskeletal 9.2% (1.6%-16%) and ocular toxicity, 3.1% range (0.3%, 6%) (Table 5), two studies were a review of literarture[25,55] and were not included and other were focused on severe ADRs, that is cutaneous[55,56], hepatoxicity[24,27,28,33]or were conducted among patients with chronic renal failure[57] which mainly focused on risk factors (Table 5).

8.5.1.2 Risk factors associated with ADR of first line DOTS regimens

The systematic review identified risk factors for ADRs among patients on first line DOTS to include the female gender (8/10 studies)[24,27,29,34,53,58–61], age > 50 years (10/11 studies)[24,27,29,30,54–56,59–61], HIV coinfection (10/10 studies)[24,27,60,61,28,29,33,47,54–56,59], pre-existing renal[5657] and liver[56272433] disease (4/4) , TB treatment duration and regimen (4/4 studies)[59273355], smoking[305953] and/or alcohol[55] (3/3 studies) , ethnicity (1/1)[34], malnutrition (3/3 studies)[59532433], cormobidities[58,59] such as diabetes (3/3)[29] and polypharmacy (3/3 studies).[29,37,56]

Nonetheless some studies did not show significant association between ADRs and female[33] gender and age[29].

Table 5: A systematic review of adverse drug reactions among patients on first line DOT regimens

Study	Population	Prevalence/ incidence	Type of ADR (prevalence)	Risk factors for ADRS
[39]Kurniawati *et al.,* 2012	TB patients (n=653) Retrospective cohort Malaysia	ADR = 103 (15.8%)	Skin reaction 51 (7.8%) Hepatotoxicity 17 (2.6%) Gastrointestinal 16 (2.5%)	
[48]AmitKumar *et al,* 2014	TB patients (n=168) Cross-sectional study India	ADRs =	Gastrointestinal (39%) Genito-urinary (32%) Musculo-skeletal (13%) Psychiatric (7%) Dermatological (6%) Vestibulo-ocular (3%) Serum bilirubin (52%) Serum albumin low 59% ESR raised 59(%).	
[58]Damasceno *et al.,* 2013	TB patients (n=176) Descriptive study Brazil	ADR all = 41.5% Total ADRs = 126 Mild ADRs = 71.4%	Gastrointestinal (29.4%) Dermatological (21.4%) Neurological (14.3%).	Female gender Age ≥ 50 years Comorbidities ≥ four Medications ≥ five
[50]Shashi *et al.,* 2014	DOTS center	ADR = 50% possible ADR = 30.6% probable Moderate = 53.2% Mild = 46.7% Severe = 0	Gastrointestinal (gastritis) Skin (Rashes).	
[36]AmitKumar *et al.*,2014	Patients (n=10083) Studies (n=8) Systematic review (2002-2012) DOTS associated ADR	ADR = 7473 (74.1%)	Dermatological 4389 (43.5%) Hepatotoxicity 1634 (16.2%) Gastrointestinal1004 (9.9%) CNS 86 (0.9%) Peripheral NS 7 (0.07%) Psychiatric in 03 (0.03%) Musculoskeletal 166 (1.6%) Otological 9 (0.09%) Ocular 29 (0.28%)	

[37]Tak *et al.*, 2009	TB patients = 94 Moderate = 31(51%) Mild ADR = 30 (49%)	ADR = 64.9% Type-A ADRs = 28.5% Type-B ADRs = 36.4%	Gastritis (87.1%) of the cases	Multiple drug therapy
[34]Sowmya *et al.*, 2017	TB patients (n=50) Descriptive	All ADR = 30(60%)	Gastrointestinal • Nausea (56%) Vomiting (30%) • Anorexia (14%) • Dyspepsia (24%) • Abdominal pain (20%), • Diarrhoea (4%) • Jaundice (8%) Malaise (16%) Skin rash (2%)	
[29]Chhetri *et al.*, 2008	TB patients (n=137) Nepal	All ADR = 54.7% (n=75) Possible ADR = 70.7% Mild ADR = 93.3%	Neurological 32 (11%)	Female Ethnicity
[29]Tavares *et al.*, 2015	TB patients (n=764) Case-control	ADR all = 55 (7.2%)	Hepatotoxicity (86.9%) Rash (8.2%) Ocular toxicity, gastrointestinal intolerance and angioedema (4.9%)	**No correlation** Age or gender **Significant association** Younger age with hepatotoxicity Diabetes mellitus
[52]Jeong *et al.*, 2009	Population = Elderly Retrospective	ADR all = 54% Major ADR = 32%	Dermatologic (9%) Gastrointestinal (8%), Arthralgia (6%) Visual change (6%) Hepatotoxicity (4%) Fever (1%)	
[59]Farazi *et al*, 2014	TB patients (n=940) TB units (n=10) Cross-sectional Iran	ADR all = 563 Minor ADR = 82.4% Major ADR = 17.6%		Females Age >50 HIV coinfection Smoking

				Retreatment TB Comorbidities
[59]Kaur *et al.*, 2015	TB patients = 114	All ADR = 95 (83.3%)	Lethargy ADR Nonspecific ADRs • Aches • Nausea, vomiting, anorexia	Females Smokers Malnourished
HIV coinfection on ADR				
[46]Marks *et al.*, 2009	TB patients = (n=331) HIV (141) vs Non-HIV Retrospective analysis for Serious ADE South Africa	ADR HIV = 26.7% ADR non-HIV = 13.3%	Peripheral neuropathy HIV = 8.3% Non-HIV = 1.9% Persistent vomiting HIV = 13.3% Non-HIV = 3.3%	HIV coinfection SAE not related to ART use
[47]Shamiya *et al*, 2015	TB patients (n=74) HIV-TB (n= 32) Non-HIV (n=42) Cross-sectional Pharmacovigilance India	ADR non-HIV = 0.36% ADR HIV/TB = 55.8%	Epigastric pain (non-HIV) Anaemia (HIV/TB)	Males HIV Urban population
[54]Lanternier *et al.*, 2007	TB patients (n=105) HIV (n= 30) non HIV (n=75) Prospective cohort	ADR incidence = 122.5 per 100 severe ADR = 45.2 per 100 py.	Hepatitis (30.5/100 py) Neuropathy (28.6/100 py)	Age >50 years HIV infection
[60]Michael *et al.*, 2016	TB patients (n=103) HIV = 30.1% Non-HIV	Mild-moderate 92%. Serious = 8 (25.5%) all in the TB-HIV co-infection		HIV status, increasing age, and female gender.
Cutaneous adverse drug reactions (cADR)				
[62]Kuaban *et al*, 1998	TB patients (n=235) TB-HIV+ (n=39), TB-HIV- (n=196) Cameroon	cADR all = 11 (4.7%) cADR HIV+ = 23.1% cADR HIV- = 1%	• Skin reactions • 2 Steven-Jonson syndrome	Pyrazinamide Rifampicin
[56]Chiang *et al*, 2007	TB patients(n=820) Retrospective design	cADR all = 47 (5.7%)	Morbiliform rash (72.3%), Erythema M/syndrome (8.5%),	HIV (27.7%) Polypharmacy (21.3%),

		pyrazinamide (2.4%) streptomycin (1.5%) Ethambutol (1.4%) Rifampicin (1.2%) Isoniazid (0.98%)	Urticaria (8.5%) Exfoliative dermatitis Lichenoid eruption	Elderly (19.1%), Autoimmune disorders (6.4%) Renal failure (4.3%), Liver disorders (4.3%).
Hepatotoxicity				
[28]Forget *et al*., 2006	Literature review Isoniazid hepatotoxicity	Incidence 9.2 per 1000 Case fatality rate of 4.7%.	Other ADRs Dermatological Gastrointestinal Hypersensitivity Neurological Hematological Renal reactions.	Advanced age
[27]Isa *et al.*, 2016	Retrospective cohort TB patients (n=110)	All ADR = 38(35%) Symptomatic • ADR = 20(18.2%) Asymptomatic • ADR = 18 (16.4%)		Low baseline ALL Low baseline bilirubin **No association** Age, sex, BMI, and duration of anti-TB treatment, HIV
[24]Tostmann *et al.*, 2008	Hepatotoxicity	Hepatotoxicity range: 2% to 28%.		Age Female sex Slow acetylator status, Malnutrition HIV Pre-existent liver disease.
[33]Moldoveanu *et al*, 2012	Hepatotoxicity risk factors			Old age Female gender Malnutrition Hypoalbuminemia, Alcohol consumption Anti-TB medication Pre-existing liver diseases Severe tuberculosis Acetylator's status

				No associations subject's age, sex and social status.
[61]Yee *et al.*, 2003	TB patients (n=430) Longitudinal study (1990 and 1999) Major adverse effects	**Incidence/100 person-months** Pyrazinamide = 1.48 Isoniazid = 0.49 Rifampicin = 0.43 Ethambutol = 0.07	Hepatotoxicity Cutaneous ADR	Female sex Age over 60 years HIV coinfection
Systematic reviews				
[61]Resende *et al.*, 2015	A systematic review Period: 1965-2012 Articles: 16 Risk factors for ADRs			Age > 60 years treatment regimens, Alcoholism Anemia HIV co-infection Low albumin NAT-2 phenotype
[25]Abhijeet *et al*, 2015	Review	ADRs = 8.0% to 85%.	**Mild ADRs** Gastrointestinal disturbances **Serious ADRs** Hepatotoxicity peripheral neuropathy, cutaneous	Multiple factors Intensive phase do not differ with intermittent or daily intake of anti-tuberculosis drugs.
Patients with renal failure				
[57]Quantrill *et al.*, 2002	Chronic renal failure TB patients = 24 cases	Pre-dialysis patients ADR = 2(35%) Dialysis patients ADR= 16 (56%)	Neuropsychiatric (6) hepatic (4) Gastrointestinal (4).	Dialysis patients

8.5.2 Hospital survey: Characteristic of the study population at the TB hospital

Out of a sample of 100 TB patients, 58% were new cases, 54% were males, 72% were co-infected with HIV and had a mean age of 41.6±13.1 (range:19-75) years (Table 1). In addition, 48% were not educated, 27% were unemployed and 57% consumed alcohol. The majority of the cases were taking the new versus the retreatment DOT regimen, 2HERZ/4HRE (55%) and were on ART co-medication (69%) (Table 1). The majority (76%) of the patients had a good adherence (≥90%) to their TB medication.

8.5.2.1 Adverse drug reactions associated with first line DOTS regimens in Namibia

Sixty-nine (69%) percent of the TB patients had at least one ADR due to first line DOTS (Table 1). The rate of ADR was significantly associated with having HIV coinfection (p=0.003), co-morbidities (i.e. opportunistic infections, p=0.047 and diabetes, p=0.019) as well as co-medications (i.e. ART, p=0.012, co-trimoxazole prophylaxis, p=0.005 and not taking antihypertensive therapy, p=0.034). There was no association between rate of ADRs of first line DOTS regimens and social demographic characteristics (i.e. female sex, advanced age and consumption of alcohol, marital status or ethnicity) as well as the treatment regimen (i.e. retreatment or new regimen) and adherence level and prior default of treatment.

Table 1: Bivariate analysis of DOTS related adverse drug reactions

Covariate	All TB cases	Occurrence of ADR		p-value
		Yes (%)	No (%)	
Prevalence of ADR	100	69(69%)	31(31%)	0.497
Age(yrs) ±SD	41.6±13.1	40.2±12.4	44.81±14.4	0.105
Body weight (kg)	46.1±8.3	44.5±6.3	48.2±11.5	0.072
Case registered				
New patient	58	42 (72)	16 (28)	0.086
Retreatment	42	27 (64)	15 (36)	
Education level				
≥ Primary education	51	5 (55.6)	4 (44.4)	0.712
No education	48	24 (68.6)	11(31.4)	
Marital status				
Married	29	20(69)	9 (41)	0.699
Not-married	71	49 (69)	22 (41)	
Alcohol consumption				
Yes	57	40 (70.2)	17 (29.8)	0.469
No	43	29 (67.4)	14 (32.6)	
Patient has diabetes				
Yes	11	4 (36)	7 (64)	0.019*
No	89	65 (73)	24(27)	
Patient has hypertension				
Yes	31	18 (58.1)	13 (41.9)	0.160
No	69	51 (73.9)	18 (26.1)	
HIV co-infection				
Yes	72	56 (77.8)	16 (22.2)	0.003*
No	28	13 (46.4)	15 (53.6)	
Opportunistic infection				
Yes	12	12 (100)	_	0.047*
No	88	57 (65)	31 (45)	
DOT regimen				
New patients	55	40 (72.7)	15 (27.2)	0.497
Retreatment regimen	45	29 (64)	16 (36)	
Medicine adherence				
>90%	76	52 (68.4)	24 (31.6)	0.632
<90%	22	15 (68.2)	7 (31.8)	
Antihypertensive therapy				
Yes	17	8 (40.1)	9 (52.9)	0.034*
No	83	61 (73.5)	22 (26.5)	
Cotrimoxazole prophylaxis				
Yes	68	53 (78)	15 (22)	0.005*
No	32	16 (50)	16 (50)	

Antiretroviral therapy				
Yes	69	53 (76.8)	16 (23.2)	0.012*
No	31	16 (51.6)	15 (48.4)	

New regimen = 2HERZ/4RHE, retreatment regimen = 2HERZS/4RH or 2HERZS/1HERZ/5HER

8.5.2.2 Grades and impact of HIV on adverse effects of first line DOT regimens

Of the 69 patients who experienced ADRs, the majority were of minor grade (i.e. grade 1 to 2) and resolved completely (n=61, 88.4%) and 8 (12%) had moderate to severe (i.e. grade ≥3) that led to hospitalization (Table 2). Adverse drug reactions of Type-A (i.e. predictable adverse drug reactions) of various grades were the most common (n=69/100, 100%). The most common Type-A ADRs were gastrointestinal, i.e. nausea and vomiting (64%) and diarrhoea (55%), musculoskeletal (i.e. joint and muscle pains or inflammation, 28%) and neuropathy (9%). The rate of Type-B (i.e. unpredictable such as allergic and hypersensitivity) adverse drug reactions was 26% (Table 2). The rate of grade ≥ 3 (i.e. liver enzyme elevation) was 34% for AST and 39% for ALT and 36% for ALP. The rate of major cutaneous ADRs was 1% with Steven Johnson Syndrome and neurological symptoms were 9%.

HIV coinfection was associated with a higher incidence of all adverse effects (p=0.002), hospitalization after ADR (p=0.022) and elevation in all the liver enzymes (p<0.05), AST, ALT and ALP as well as the occurrence of Nausea and vomiting (p=0.006), ocular toxicity (p=0.042) and inflammatory response (p=0.022) (Table 2).

Table 2: Grades and impact of HIV on adverse effects of first line DOT regimens

	HIV coinfection		Total	χ^2	df	p-value
	Yes	No				
Experienced ADR	56 (81.2%)	13(18.8%)	69(100.0%)	9.3	1	0.002*
Yes	16(51.6%)	15(48.4%)	31(100.0%)			
No						
Outcome of the ADR	7(87.5%)	1(12.5%)	8(100.0%)			
Hospitalized	45(86.5%)	7(13.5%)	52(100.0%)	7.6	2	0.022*
Resolved	5(50.0%)	5(50.0%)	10(100.0%)			
No effect						
AST elevation(iu/L)	30(61.2%)	19(38.8%)	49(100.0%)			
Grade 1	4(57.1%)	3(42.9%)	7(100.0%)			
Grade 2	6(100.0%)	0(0.0%)	6(100.0%)	10.9	4	0.028*
Grade 3	26(86.7%)	4(13.3%)	30(100.0%)			
Grade 4	4(100.0%)	0(0.0%)	4(100.0%)			
ALT elevation (iu/L)	33(61.1%)	21(38.9%)	54(100.0%)			
Grade 1	3(100.0%)	0(0.0%)	3(100.0%)			
Grade 2	20(87.0%)	3(13.0%)	23(100.0%)	8.9	3	0.030*
Grade 3	14(87.5%)	2(12.5%)	16(100.0%)			
Grade 4						
ALP elevation (iu/L)						
Grade 1	15(62.5%)	9(37.5%)	24(100.0%)			
Grade 2	23(63.9%)	13(36.1%)	36(100.0%)	8.0	3	0.046*
Grade 3	15(83.3%)	3(16.7%)	18(100.0%)			
Grade 4	17(94.4%)	1(5.6%)	18(100.0%)			
Ocular toxicity	10(100.0%)	0(0.0%)	10(100.0%)			
Yes	58(69.9%)	25(30.1%)	83(100.0%)	4.1	1	0.042*
No						
Anaemia grade						
Normal	13(65.0%)	7(35.0%)	20(100.0%)			
Grade 1	8(66.7%)	4(33.3%)	12(100.0%)			
Grade 2	39(73.6%)	14(26.4%)	53(100.0%)	1.5	3	0.685
Grade 3	10(83.3%)	2(16.7%)	12(100.0%)			
Leukopenia grades	41(69.5%)	18(30.5%)	59(100.0%)			
Grade 3	29(76.3%)	9(23.7%)	38(100.0%)	0.5	1	0.464
Grade 4						
Nausea and vomiting	52(81.3%)	12(18.8%)	64(100.0%)			
Yes	20(55.6%)	16(44.4%)	36(100.0%)	7.5	1	0.006*
No						
Diarrhoea	43(78.2%)	12(21.8%)	55(100.0%)			
Yes	29(64.4%)	16(35.6%)	45(100.0%)	2.3	1	0.128
No						
Allergic reactions	22(84.6%)	4(15.4%)	26(100.0%)			
Yes	50(67.6%)	24(32.4%)	74(100.0%)	2.8	1	0.096
No						
Steven Johnson syndrome	1(100.0%)	0(0.0%)	1(100.0%)			
Yes	71(71.7%)	28(28.3%)	99(100.0%)	0.4	1	0.531
No						
Peripheral neuropathy	7(77.8%)	2(22.2%)	9(100.0%)			
Yes	65(71.4%)	2628.6%)	91(100.0%)	0.2	1	0.686

No						
CNS adverse effects Yes No	1(100.0%) 71(71.7%)	0(0.0%) 28(28.3%)	1(100.0%) 99(100.0%)	0.4	1	0.531
Arthralgia Yes No	23(82.1%) 49(68.1%)	5(17.9%) 23(31.9%)	28(100.0%) 72(100.0%)	1.9	1	0.159
Inflammatory response Yes No	27(87.1%) 44(64.7%)	4(12.9%) 24(35.3%)	31(100.0%) 68(100.0%)	5.3	1	0.022*

8.5.2.3 Effect of DOTS on liver enzyme elevation and blood cell counts

Moderate to severe elevation of liver enzymes, i.e. Aspartate amino transferase (AST) and Alanine amino transferase (ALT) was observed in the first months of therapy but decline to normal levels at months three of treatment (i.e. 0 – 40 iu/L) (Table 3). On average, there was a significant three to four-fold elevation in the liver enzymes (AST and ALT) in the first month after initiation of DOTS regimens and this normalized by the third month (Table 2). However, the mean hemoglobin and albumin levels declined at months three relative to the baseline (Table 3).

Table 3: Effect of DOTS on liver enzyme elevation and blood cell counts

Covariate	Baseline (mean±SD)	3 months (mean±SD)	p-value
ALT (iu/L) (n=94)	141.4 ±111.5	23.5±10.3	0.000*
AST (iu/L) (n=96)	178.2 ±130.9	38.0 ±12.9	0.000*
ALP (iu/L) (n=96)	41.2 ±27.2	50.2 ±38.6	0.253
Albumin (g/dL) (n=94)	23.5 ±6.4	18.3 ±4.6	0.006*
Haemoglobin (g/dL) (n=97)	5.4 ±3.5	3.3 ±3.6	0.008*

ALT = alanine amino transferase, AST= Aspartate amino transferase, ALP = Alkaline phosphatase
NB: Baseline measurements were taken at start of the TB treatment

8.5.2.3 Predictors of adverse effects for first line DOTS regimens in Namibia

A logistic regression analysis was conducted for each covariate to identify predictors of adverse drug reactions for first line DOTS regimen using crude odd ratios (cOR) (**Table 4)**. The Wald criterion demonstrated that; TB patients registered as relapse OR=4.9(95%CI:1.2,19.7), HIV coinfection OR= 4.0(95%CI: 1.6,10.2) and co-medication with cotrimoxazole preventative therapy OR=3.5(95%CI: 1.4,8.7), anti-retroviral therapy and antihypertensive therapy made a significant contribution to prediction of occurrence of ADRs related to first line DOTS regimens. However, no significant impact of the treatment regimen, the patient's socio-demographic characteristics (i.e. age and sex), other co-morbidities, body weight with occurrence of ADRs related to first line (Table 4).

Table 4: A multivariate model for predictors of adverse effects for first line DOTS

	B coeficient	Standard error	Wald	df	cOR (95%CI)	p-value
Patients gender						
Female	-0.3	0.43	0.6	1	0.7(0.3,1.7)	0.451
Male					1	
Age(years)	0.03	0.01	2.6	1	1.0(0.9,1.1)	0.107
Tuberculosis category			6.1	3		0.106
New	0.4	0.58	0.4	1	1.5(0.5,4.5)	0.525
Relapse	1.6	0.71	4.9	1	4.9(1.2,19.7)	0.026*
Failure	1.3	1.50	0.8	1	3.8(0.2,72)	0.374
Default				1		
Body weight (kg)	0.1	0.03	3.2	1	1.1(0.9,1.1)	0.075
Tuberculosis case						
New	-0.6	0.44	1.9	1	0.6(0.2,1.3)	0.170
Retreatment					1	
Cotrimoxazole prophylaxis						
Yes	1.3	0.46	7.6	1	3.5(1.4,8.7)	0.006*

No					1	
Antiretroviral therapy						
Yes	1.1	0.46	6.1	1	3.1(1.3,7.6)	0.014*
No					1	
Antihypertensive therapy						
No	-1.1	0.55	4.3	1	0.3(0.1,0.9)	0.037*
Yes					1	
Adherence to TB medication	0.01	0.52	0.0	1	1.0(0.3,2.8)	0.983
Yes					1	
No						
HIV coinfection						
Yes	1.4	0.47	8.7	1	4.0(1.6,10.2)	0.003*
No						
Tuberculosis regimen						
2RHEZ/4RHE	0.2	0.22	0.8	1	1.2(0.8,1.9)	0.374
2RHEZS/1RHEZ/5RHE						

8.6 Discussion

To our knowledge, this is the first hospital-based study to describe the burden of adverse drug reactions among patients on first line DOTS regimens in Namibia compared with the global rates. The hospital-based study found a high prevalence of ADR among patients on DOTS regimens relative to other studies by Archana Saha *et al*. (54.7%) , Amitkumar *et al* (11.6%) and the systematic review that reported a mean prevalence of 50.1±21.9%.[23,29,63]This is due to the fact that 72% of the patients in our study were co-infected with HIV, a risk factor for drug-disease and drug-drug interactions with TB medication. Nevertheless our findings are within the range of the estimated prevalence of ADR in the systematic, range (7.2%-83.3%). However, though the rate of ADRs in our study is lower than another study conducted in Namibia by Sagwa *et al.* (i.e. 90%) among 59 patients on second line TB- medication for MDR-TB in Namibia.[23,29,63] This is not surprising as second line TB regimens are associated with lower safety profiles than first line DOTS regimens.[64]

The hospital-based study graded the majority of the ADRs as mild and were related to gastrointestinal, immunological reactions, neurological and liver enzyme elevation. This finding is in agreement with the systematic review we conducted that reported the occurrence of mild ADR at 72.5±20.6% (46.7%-93.3%) compared to moderate or severe. Nonetheless the rate of serious adverse effects in the hospital study (21.6%) and the systematic review are high and this call for interventions to continually monitor and prevent the occurrence in high risk populations.

The findings on the type of adverse effects are comparable across the systematic review and other studies that report gastrointestinal, musculoskeletal and neurological adverse effects as the most common. These are indeed the predictable adverse effects of the first-line TB medication, associated with gastrointestinal effects (RHZE), hepatotoxicity (RHZ), neurological effects (H) and musculoskeletal effects (Z). However, the occurrence of gastrointestinal ADR in the hospital-based study was higher than reported by Sagwa *et al.* (range: 9-23%) and Amitkumar *et al* (23.8%) as well as the mean prevalence in the systematic review. This may perhaps related to other risk factors such as dosage regimen, co-medication and inter-population variability, among other factors. The frequency of allergic/inflammatory ADRs in the hospital based study was comparable to findings by Amitkumar *et al.* (28.5%) and the systematic review and may be related to the high incidences of HIV in both studies.

The occurrence of peripheral neuropathy (9%), this was lower than that reported by Archana *et al* (18.57%). Peripheral neuropathy is mainly attributed to isoniazid, and patients categorized as slow acetylators are at high risk for isoniazid induced neuritis. We are currently investigation the distribution of NAT-2 polymorphism in the Namibian population in order to establish the appropriate dosing for INH in this population. The incidence of inflammation ADR was thrice higher than reported Amitkumar *et al*. (9.5%) and also higher than the mean in the systematic review. Indeed, this variability may be attributed to the burden of inflammatory diseases including HIV in our setting with a high disease burden. Secondly, our study recruited patients who were hospitalized, and are likely to have other inflammatory diseases.

The hospital-based study showed that the occurrence of DOTS related ADR was significantly related with HIV co-infections, having opportunistic infections and co-medication with anti-retroviral (ARV) and body low bodyweight. The systematic review we conducted and similar studies by Shaoweng *et al.* and AmitKumar *et al.* also reported higher ADR among cases with weight less than 48kg and with HIV coinfection (80.6%).[63] The occurrence of adverse drug reactions is attributed to drug-drug interactions as a result of additive effects such as with hepatotoxicity with TB and ART medication as well as with HIV associate immune reconstitution syndrome. In the hospital-based study, patient socio-demographic characteristics including male gender and age, alcohol intake as well as case categorization as new/retreatment were not significant predictors of occurrence of ADR in the Namibia population. This is contrary to findings by Shaoweng *et al.* who reported a higher occurrence of ADR among cases aged between 29-55 and the educated

and alcohol use.[29,65] Even, then the findings on the role of age and sex are conflicting across stoic dies included in the systematic.

The study has several limitations these include a small sample size and several confounding factors such as other co-medication with home medicines and herbals, patient diet and severity of the TB, laboratory variables and co-infections. Secondly the retrospective design associated with missing data on variables and this may lead to bias in the interpretation the findings as only hospitalized patients were included in the study. Nevertheless, the hospital-based study and systematic review provides preliminary findings on current safety profile of first line DOTS regimens which has been shown to impact treatment outcomes.

In conclusion, the study clearly demonstrated that there is relatively high rate of adverse effects of anti-tuberculosis medicines in patients who are initiated on first line TB regimens. The study also found out the type of adverse effects that are most common in patients on tuberculosis treatment and also the grades of these adverse reactions. The study also found out that the most common types of adverse events associated with anti-tuberculosis medicines include specific GIT-related adverse effects like diarrhea, vomiting and nausea, and some of the adverse reactions include inflammation allergies and hepatotoxicity.

This study found that adverse events of varying severity, most commonly occur during the initial phase of treatment, which is usually in the first 3 months of treatment. Some adverse events were more prevalent in TB patients co-infected with HIV and patients who were taking antiretroviral treatment and cotrimoxazole. The characteristics,magnitude of risks and factors asscoiated with these adverse drug events should be examined in further studies using either cohort studies or prospective studies together with active surveillance pharmacovigillance. Also because of the high incidence of adverse drug events it is important that health professionals including doctors, nurses and pharmacists closely monitor and manage ADRs during the intensive phase of treatment as poor management of these adverse events can lead to poor adherence from patients, morbidity and death of a patient as some of these adverse events are relatively common. There is a need to strengthen active surveillance and reporting pharmacovigilance framework within the DOTS programmeme in Namibia.

Conflict of interest and funding

The authors hereby declare that they have no conflicts of interest to disclose. This study did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Acknowledgements

The authors wish to acknowledge the assistance rendered by the staff at the outpatient departments of Katutura State hospital, Ministry of Health and Social Services in collection of the data.

Author contributions

DK played the leading role in conceptualizing, data collection, analysis and write up of the manuscript. TT conceptualized and assisted in data collection. TR, RV and BG edited and appraised the paper during the various stages of publication. All authors permitted the submission of this paper to this journal.

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CHAPTER 9: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

9.1 General discussion

9.1.1 Overview of the model for optimizing TB treatment success rates

This study aimed to develop a model for optimizing TB treatment success rates in Namibia (Figure 1). The model is synthesis of findings of the studies on predictors of tuberculosis treatment success rates in Namibia, i.e. Chapter 3 through Chapter 8. Only significant population, patient and drug level predictors of treatment success rates are included in the model. The model also illustrates the complex inter-relationship between the population, patient and drug level covariates. Indeed, the predictive models highlights the challenge that TSR in Namibia have stagnated below the 90% global targets and that the current interventions may not be adequate to optimize TB treatment success rates by 2035 and/or in Namibia.

From his model we derive conclusions and recommendations for improving tuberculosis treatment success rates in Namibia and related settings. In summary, the following recommendations to improve TB treatment success rate; (a) Comprehensive integration of HIV and TB care services, (b) Mandatory screening and access to resistance testing, (c) Strengthen HIV/TB case-management in CB-DOTS, (d) Screening for rifampicin/ ethambutol serum levels. (e) Follow-up bacteriological testing for cases evaluated by treatment completion. (f) Model the population dynamics of TB incidence. (g) Strengthen social welfare, pharmacovigilance and TDM services in TB care and (h) Advocacy for work-based DOTS services

9.1.2 A model for optimizing TB treatment success rates in Namibia

To our knowledge, this is the first study to systematically assess and comprehensively model TB treatment success rates in a high tuberculosis burden setting across all patient categories of drug sensitive tuberculosis as well as at the population and DOTS treatment regimen levels. In addition, the study is the first to demonstrate the use of an interrupted time series methodology to model the impact of the WHO's Directly Observed Treatment Short course (DOTS) strategy and population-level time varying covariates on tuberculosis treatment success rates in a high TB burden setting.

Indeed, the final model (i.e. Figure 1 below) shows that community-based DOTS effectively increased treatment success rates or cure and treatment completion for both patients with pulmonary and extrapulmonary tuberculosis as well as cases with drug resistant tuberculosis (Chapter 2.1). These findings are consistent with those of Wright *et al*., who conducted a systematic review that also showed that CB-DOTS had an impact of 1.54 (1.01–2.36; $p = 0.046$) compared to facility-based DOTS. The final model in (Figure 1, below) has potential to be integrated in DOTS programmes worldwide in an effort to end tuberculosis by 2035. The final model depicts an interplay between population, patient and DOTS regimen predictors on treatment success rates (Figure 1).

Figure 1: Conceptual model for optimizing tuberculosis treatment success rate

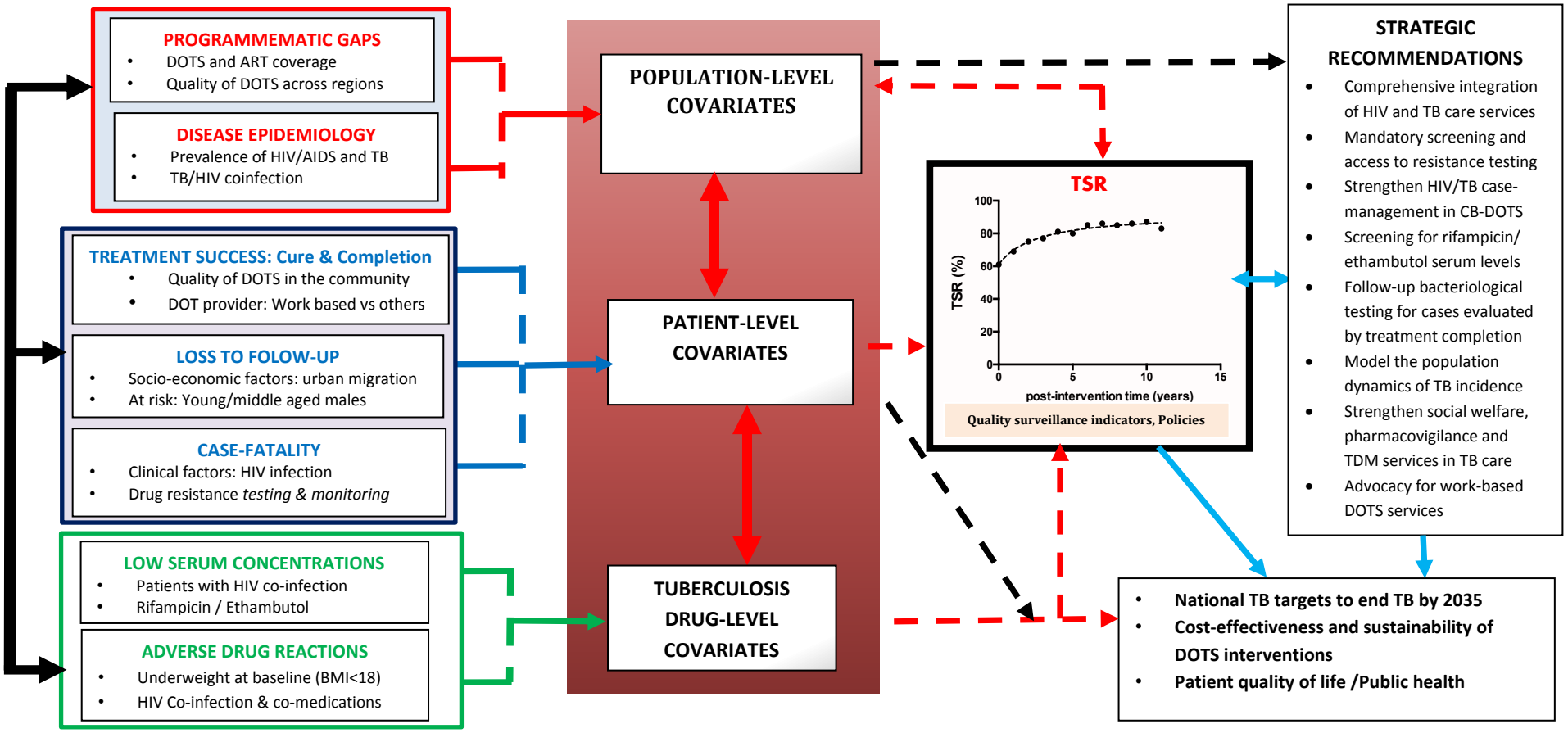


Figure 1: above shows a conceptual frame work demonstrating the relationship between the population-level, patient-level and drug level predictors on treatment success rates and strategic recommendations to optimize outcomes.

9.1.3 Ending tuberculosis in Namibia by 2035

Firstly, based on the findings in the predictive model (Chapter 2.1, final model), the study concludes though CB-DOTS effectively improved treatment success rates in Namibia, the programme is insufficient to attain the global treatment success targets to end TB by 2035. However, unlike the previous studies, our study also demonstrates the impact of the DOTS over time, which depicts a stagnation of tuberculosis TSR below 90% global thresholds for five years (2013-2017) after implementation of the CB-DOT programme. This stagnation in TSR and/or cure rates is an important barrier to end TB in Namibia by 2035. Indeed, this calls for efforts to improve on the quality and quantity of the current interventions to optimize treatment outcomes and end TB in Namibia.

Moreover, the ITS model also demonstrates that several population-varying covariates particularly prevalence of HIV negatively impacts on TSR mainly among patients with drug sensitive TB whilst access to quality DOTS and antiretroviral therapy as having a positive impact (Chapter 2.1: Figure 4 and Table 2). On the contrary, the model suggested that the declining CNR in tuberculosis did not appear to impact on treatment success rates. Despite the decline, the CNR in Namibia remains above the global target of 300 cases per 100 000, this is high given the limited capacity and resources to provide consistent quality care at each DOTS point in every region of Namibia. The study suggest that ITS modeling provides a real time assessment of effectiveness of DOTS programmes and could be validated and adopted by National Tuberculosis Programmes across countries to assess the impact of interventions in order to improve TB indicators and outcomes to end tuberculosis by 2035.

9.1.4 HIV coinfection negatively affects treatment success rates

Secondly, based on our findings, the final model affirms reported evidence that HIV is the main predictor for sub-optimal tuberculosis treatment success rates across the three levels, i.e. population, patient and tuberculosis drug therapy (Figure 1). The population prevalence and co-infection with HIV among TB patients significantly reduced the annual trend and level of the aggregated national treatment success (Chapter 3), as well as cure and completion rates (Chapter 4).

The ITS model of the population treatment success rates showed that HIV prevalence and co-infection significantly reduced national annual trends in treatment success, cure and completion rates by up to 4.4 % annually among cases with drug sensitive TB (Table 2, Chapter 3). Furthermore, HIV increased the risk of tuberculosis case-fatality by up to 80% (Chapter 6), sub-therapeutic serum levels for rifampicin and ethambutol (Chapter 7) as well as adverse reactions associated with the use of first line DOT regimens (Chapter 8). Moreover, the patient level models for treatment success rates affirm that HIV affects negatively on tuberculosis cure and treatment completion rates as well as case-fatality. Patients without HIV co-infection are 80% less likely to die while on DOT therapy (Chapter 6), and HIV positive patients are 80% less likely to have a successful treatment (i.e. cure or treatment completion) compared to HIV negative patients (Chapter 4).

Furthermore, the prevalence of lower serum levels of first line anti-tuberculosis drugs (i.e. rifampicin and ethambutol) as well as adverse effects are more common among patients with HIV coinfection than those without. The negative impact of HIV on treatment success

is a concern, and supports the move towards comprehensive integration of HIV and TB programmes in order to optimize surveillance, case management (including therapeutic drug monitoring and pharmacovigilance) and treatment outcomes.

9.1.5 Programmatic implications for optimal treatment success rates

Thirdly, we conclude from the final model that the programmatic implementation of DOTS services varies across the 14 geopolitical regions of Namibia and DOT access points (i.e. DOT support), and influences the optimization of tuberculosis TSR (Chapter 3.1 and Chapter 2.1). For instance, the nation-wide access to community-based DOTS and anti-retroviral therapy in the 14 regions of Namibia significantly improved TB treatment success rates. In addition, the work-based DOT support was more effective (i.e. 2.5 times higher impact) on improving treatment success compared to other forms of treatment support, that is community person, guardian (i.e. relative and neighbor) and facility.

These findings suggest that TB programme in Namibia should ensure a consistent access to quality DOTS services at all levels of implementation (i.e. national, region, health district and DOT access points). The study therefore concludes that Namibia achieving universal coverage for DOTS and ART services, the inequitable access to a comprehensive package of the services is a barrier for providing quality care and improving treatment outcomes. Moreover, the treatment outcome for a significant number of patients under the CB-DOTS programme is reported as either *"not available"* in the electronic TB register or treatment success as treatment completion rather than cured. A significant proportion of TB patients who complete treatment has no clear treatment end-points determined.

There is no system to assess the quality of and to validate the use of treatment completion as a reliable yardstick of treatment success. The findings suggest the need for an efficient system to optimize sputum and drug resistance testing within the community-based DOTS (Chapter 3.1 and 3.3). Similarly, the lack of a system to conduct follow-up bacteriological as well as drug resistance testing among patients that complete treatment is a major hurdle, among others, in the DOTS programme towards optimizing treatment success rates. The study proposes follow-up sputum and drug resistance testing at one month following completion of treatment.

Furthermore, the study demonstrates the need for a social-economic support structure to minimize loss to follow-up, particularly among high-risk groups. From the study, it is apparent that unemployment among the youth-middle aged males is the main driver of LTFU in Namibia. This population has the highest unemployment rate, the highest risk of HIV-infection, and urban migration (i.e. move between towns to seek for employment and/or career opportunities). Moreover, the study demonstrates that work-based DOT support has the highest impact on improving TSR (Chapter 3.2). The TB programme in Namibia should advocate for work-based DOTS services and/or create temporary employment opportunities for this high-risk population to enhance treatment completion and outcomes.

9.1.6 Case-management and follow-up critical for optimal treatment success rates

Fourthly, the study demonstrates the need to strengthen the TB case management under the community-based DOTS programme in Namibia. The patient-level models for

treatment success rates in Namibia affirms previous findings that HIV coinfection and ART co-medication, i.e. Highly active antiretroviral therapy (HAART) and cotrimoxazole preventive therapy (CPT) are independent predictors of treatment success. There is a need for research to determine clinical, biological and pharmacokinetic thresholds for TSR among HIV co-infected patients populations in Namibia.

On contrary, we found that patient socio-demographic characteristics such as gender and age are not significant predictors of treatment success (i.e. cure and completion) under the DOTS programme in Namibia. This finding differs from several studies in Africa that identify the male gender as a risk factor for poor treatment outcomes (Chapter 3.1and 3.3). However, a sub-analysis of the treatment outcomes showed that socio-economic factors were independent drivers of loss to follow-up (LTFU), that is young and/or middle-aged male patients, living in migratory towns were at increased risk of LTFU. Moreover, this study affirms the finding from the Namibia National Health survey young and/or middle age males are is at high risk for contracting HIV, urban migration, unemployment and alcohol abuse, which are important barriers to TB medication adherence and outcomes. This suggests the need for targeted and/or integrated interventions to incorporate social-economic measures to incentivize high-risk group to minimize LTFU.

Whereas socio-economic factors were the main determinants of LTFU, patient clinical characteristics, that is HIV coinfection and drug resistance testing, are the only independent predictors for case-fatality among patients diagnosed with drug sensitive tuberculosis. This is a concern as several studies have linked poor access to drug resistance

testing with tuberculosis drug resistance among HIV patients, partly due to sub-therapeutic levels due the poor pharmacokinetics (i.e. poor absorption) of TB medicines, among other factors. In addition, the interaction between HIV and TB disease as well as the TB and HIV co-medications are important drivers for life threatening adverse drug reactions such as hepatitis and immune reconstitution syndrome. Thus, there is a need for further studies to determine the biological and clinical thresholds for poor outcomes including death in order to guide the case-management of patients at risk. This study affirms the negative impact of HIV on serum concentrations for rifampicin and ethambutol in the African population.

9.1.7 Integration of pharmacovigilance and therapeutic drug screening in DOTS

Lastly, the meta-analysis affirms findings from previous studies, i.e. the negative impact of HIV coinfection on the maximum serum concentration (C_{max}) of all first line TB medicines, the reduction was more significant for rifampicin (R) and ethambutol (E) in the African population (Chapter 4.1). Similarly, the study depicts a variability in the impact of HIV on serum concentrations of first line antituberculosis medicines across studies among the African population with majority of the studies reporting low mean levels for rifampicin, isoniazid, ethambutol and pyrazinamide.

This confirms the initial hypothesis that patients in Africa with or without HIV coinfection are at risk of sub-therapeutic serum concentrations of first line antituberculosis medicines. Nevertheless, the impact of sub-therapeutic serum levels of TB medicines on treatment

success rates in HIV and other groups remains controversial and unknown in the African population.

The study describes a high burden of adverse drug effects among patients on first line DOT regimens in Namibia. The majority of the adverse effects were type "A" (i.e. predictable adverse drug reactions) and of a mild grade (i.e. grade 1 and 2). Similarly, elevation in the liver enzymes (i.e. ALT and AST) was 3 times the upper limit of the normal range during the first month of treatment, but subsided to normal by 3 months. The occurrence of moderate to severe adverse drug reactions (i.e. grade 3 and grade 4) such as Stevens Johnson syndrome (SJS), although low (<5%), but clinically significant because they are challenging to manage and have poor prognosis. Similarly, a significant number of patients experienced Type-B adverse drug reactions, i.e. unpredictable allergic or hypersensitivity drug reactions. Adverse drug reactions affect the adherence to medication and interrupt treatment and treatment outcomes.

9.1.8 General limitations

The author accepts that the research studies in this thesis may have some limitations. For instance, we were unable to assess the impact of some population level covariates such as funding, availability of medicines and quality and capabilities of human resources on care and treatment success rates. In addition, in some studies, secondary data was used and some covariates with missing data. Nevertheless, the study gives a systematic and comprehensive assessment (i.e. population-level, patient-level and TB drug level of the determinants of treatment success rates and gives a true reflection of routine practice in

Namibia. More so, the study identifies critical programmatic gaps in the current DOTS interventions based on nation-wide data aggregated over a 10-year period. As a result, we believe that our findings are important in providing evidence, which can guide efforts to improve treatment success rates among high-risk populations.

9.2 Conclusions

Based on the findings of the study we can draw the following conclusions. Firstly, Community-based DOTS is an effective strategy that improved treatment success rates across all forms of tuberculosis in Namibia. The interrupted time series modeling is a comprehensive design for evaluating the effectiveness of the DOTS interventions on treatment success rates. However, the CB-DOTS is not sufficient to reach the 90% TSR target under the End TB strategy. The main population covariates are programmatic access and/or integration of HIV/TB services including quality and coverage for DOTS and ART.

The main patient-level predictors of TSR were programmatic (i.e. the regional implementation of DOTS programme) as well as clinical, i.e. treatment for HIV/AIDS and/or tuberculosis and cotrimoxazole prophylactic therapy. This calls for the integration of HIV/TB programmes and services at all levels in order to optimize treatment success rates in Namibia. In addition, the main predictors for LTFU were social-economic factors, namely young/middle aged men in business or border region, and this is a high-risk group to unemployment and urban migration as well as HIV that are important barriers to access to TB care and adherence to therapy. The main predictor of death of TB cases in the DOTS

programme is clinical, i.e. HIV coinfection, access to drug resistance and/or sputum smear testing.

9.3 Recommendations

It is apparent from the study that TSR are sub-optimal, and that HIV coinfection, programmatic as well as patient socio-economic and clinical characteristics are the main determinants of TSR in Namibia. The following recommendations should be implemented towards optimizing tuberculosis treatment success rates in Namibia:

9.3.1 Managerial/programmatic interventions

The study affirmed that treatment success rates varied by region and access to certain DOTS services (i.e. sputum and drug-resistance testing) were not consistent across regions and/or DOT sites. In addition, treatment success rates were determined by treatment completion than cure. Therefore, we recommend that the National TB programme to ensure that a comprehensive package of quality DOTS services is provided at all DOTS access points within the community. It was apparent that access to bacteriological and drug-resistant testing is a major barrier to evaluation of treatment success rates under the community-based DOTS approach. The study recommends implementation of community-based technologies and/or a system to enhance sputum and drug resistance testing in the community. There is also a need to improve follow up sputum and drug-resistance testing for patients whose treatment success rates are determined by treatment completion.

9.3.2 Policy implications

The study showed that HIV is a critical determinant of treatment success rates at population, patient and TB drug therapy levels. The Ministry of Health and Social Services should develop and implement a comprehensive framework to integrate HIV and TB care and services at all levels, i.e. integrate policies, care and resources.

9.3.3 Follow-on studies

The National Tuberculosis and Leprosy Programme should incorporate strategic research goals to: (a) Model the epidemiology of the various types of tuberculosis (i.e. drug sensitive and drug resistant) in Namibia in order to equitably allocate resources and targets to end tuberculosis in the country. (b) To determine the prevalence, determinants and impact of sub-optimal plasma levels of first line TB medications on the treatment success rates (i.e. cure rates) and adverse effects in patients with/without HIV co-infection. (c) To estimate impact of access to drug resistant TB testing on case-fatality rate. (d) To determine the cost-effectiveness of the various models (i.e. Facility-based and community-based) of DOTS programme since its implementation in 1995. (e) To assess the validity and reliability of treatment completion as a measure of treatment success.

9.3.4 Educational interventions

It is clear that HIV has a negative impact on treatment success rates. To strengthen the capacity among staff in both the HIV and TB programmes in Namibia. In particular, strengthening on quality assurance processes for TB case identification and management, as well as evaluation and reporting of treatment outcomes. More emphasis should be

placed on bacteriological and drug resistance testing as well determination of treatment outcomes.

9.3.5 Social welfare

Tuberculosis treatment is long term and we have identified socio-economic drivers for LTFU. There is need for equitable access to social grants for groups (i.e. unemployed young-middle aged male) at high risk of LTFU and poor outcomes in order to optimize drug therapy. In addition, there is a need for a mobile platform to effectively track cases lost to follow up. The study also recommends the integration of temporary employment opportunities within CB-DOTS programme for patients at risk of LTFU and advocate for treatment models that advocate the integration of DOTS services in workplaces.

9.3.6 Advocacy

The study showed that TSR varied across regions. The National TB and Leprosy programme should advocate for minimum targets for each DOTS site, region and health district in order to optimize the quality of case management and DOTS services across are TB programmes in all regions. In addition, there is need for the NTLP to increase the awareness of minimizing loss to follow-up and other poor outcomes. The NTLP should advocate for a 90% target for TSR rate based on 90% cure rates at all levels (i.e DOT site, district, regional and national).

9.4 Contributions

This study has made significant contributions to the body of knowledge and research on tuberculosis world-wide, that is:

- **A novel methodology (i.e. interrupted time series design)** to systematically and comprehensively evaluate the impact of the DOTS interventions and population time varying covariates on treatment outcomes in a high TB burden setting. This methodology has the potential to be adapted by TB programmes worldwide to evaluate the effectiveness of the interventions in order to meet the global targets.
- **An overall model to guide TB programmes** worldwide on the critical aspects that drive TSR as well as strategic recommendations to be adapted in national TB medium- and long-term plans to improve treatment success rates.
- **Knowledge and research direction**, the study has described for the first time the predictors of TSR in Namibia at three levels, that is population, patient and TB drug level. In particular the study provides future research plans to optimize treatment success rates globally.
- **Policy direction,** the study has identified programmatic obstacles towards optimizing treatment success rates, namely quality of DOTS services across all levels of care, groups at high risk of poor treatment outcomes, that is HIV co-infected patients, access to sputum and resistance testing, as well as young-middle aged males prone to urban migration.

APPENDICES

APPENDIX A: National Strategic Plan on Tuberculosis (MTP-I and II)

	MTP-I: First Medium-Term Strategic Plan for TB	MTP-II: Second Medium Term Strategic Plan for TB
Strategic result 1	Treatment success (cure + completion) rate increased from 65% to 85% for all patient categories by 2009 • NTCP started rolling out CB-DOT in 2005 • Introduction of Fixed Dose Combinations (FDCs) for first line tuberculosis treatment	High quality TB DOTs and leprosy services expanded and enhanced, • Review of TB treatment guidelines from 2RHZE/4RH to 2RHZE/4RHE • TSR of 87% achieved for all patient categories on first line treatment • Uninterrupted supply of TB medicines
Strategic result 2	All tuberculosis suspects and patients have access to timely and quality-assured TB laboratory services	2. Increased access to high quality TB/HIV treatment and care intervention,
Strategic result 3	Adequate and competent human resources for TB control at all levels	3. Programmatic management of drug-resistant TB improved and scaled up, • DOT system for DR-TB patients
Strategic result 4	Management capacity of National Tuberculosis Control programme (NTCP) strengthened and adequate at all levels	4. General health systems strengthened and effectively supporting TB and leprosy services,
Strategic result 5	Operational research and epidemiological surveillance capacity in place and supporting management and M&E	5. Partnership for TB control and leprosy eradicated strengthened, and
Strategic result 6	80% of the general population have a satisfactory level of knowledge on tuberculosis disease and services for appropriate health-seeking behaviour	6. Communities and people with TB and leprosy empowered.
Strategic result 7	All PLWHA and PLWTB have access to a continuum of care and support services for TB and HIV/AIDS, in all health care facilities and home-based care services in public and private sector by 2009	
Strategic result 8	Financial resources for TB control in public and private sector are adequate	
Strategic result 9	Specific TB control strategies implemented in sectors with high tuberculosis burden by 2009	

Adapted from the Medium Term Plan (MTP-I and MTP-II) ;
***MTP-I (2004-2009)**: Based on the DOTS strategy and **MTP-II (2010-2015)**: Based on the Stop TB strategy and the Enhanced Global strategy*

APPENDIX B: Data abstraction tool for the hospital based study for predictable of TB case fatality and burden of adverse drug reactions

Retrospective cohort analysis of risk factors for unsuccessful treatment outcomes to standard first line TB treatment (RHEZ) in Namibia

Respondent unique ID #: _____ Data collector Name: _____
INTNAME

Data collection Date: ___/____ /_____
INTDATE

DD/MM/YYYY

<table>
<tr><th colspan="8">PART A: PATIENT'S SOCIO-DEMOGRAPHIC CHARACTERISTICS</th></tr>
<tr><td>101 Age (years)

_____</td><td>102. Sex
Male (1)
Female (2)</td><td>103.Pregnant
Yes (1)
No (2)</td><td>104.Marital status
Single (1)
Married (2)
Widowed (3)</td><td colspan="2">105. Education level
Primary (1)
Grade 10 (2)
Grade 12 (3)
Diploma (4)
Graduate (5)</td><td colspan="2">106. Region of birth
Erongo (1)
Hardap (2)
//Karas (3)
Kavango east (4)
Kavango west (5)
Khomas (6)
Kunene (7)
Ohangwena (8)
Omaheke (9)
Omusati (10)
Oshana (11)
Oshikoto (12)
Otjizojupa (13)
Zambezi (14)</td></tr>
<tr><td colspan="4">107. Employment status
Formal employment (1)
Casual employment (2)
Self-employed (3)
Un employed (4)</td><td colspan="4"></td></tr>
<tr><td colspan="3">108. Patient smokes
Yes (1) : # cigarettes / week: _____
No (2)</td><td colspan="3">109. Patient takes alcohol
Yes (1) # bottles week: _____
No (2)

If yes state the Type of alcohol
_____</td><td colspan="2">110. Tribe
Oshiwambo (1)
Damara/Nama (2)
Africans (3)
Herero (4)
Caprivian (5)
Other: _____</td></tr>
<tr><th colspan="8">PART B:PATIENT'S MEDICAL BACKGROUND</th></tr>
<tr><td colspan="3">111. Tuberculosis diagnosis TB Symptoms: Yes (1) No (2)
Smear positive: Yes (1) No (2)
ZN positive : Yes (1) No (2)</td><td colspan="2">112. HIV co-infection
Yes (1)
No (2)</td><td>113. Liver disease
Yes (1)
No (2)</td><td colspan="2">114. Renal disease
Yes (1)
No (2)</td></tr>
<tr><td colspan="3">115. Gastrointestinal disease
Diarrhoea Yes (1) No (2)
Absorptive disease Yes (1) No (2)
Other: _____</td><td>116. Diabetes mellitus
Yes (1)
No (2)</td><td colspan="2">117. Hepatitis infection
HBV Yes (1) No (2)
HCV Yes (1) No (2)</td><td colspan="2">118. Hypertensive
Normal BP (1)
Stage 1 HTN (2)
Stage 2 HTN (3)
Stage 3 HTN (4)</td></tr>
<tr><th colspan="8">PART C: MEDICATION HISTORY</th></tr>
<tr><td colspan="2">119. Ever taken TB meds</td><td colspan="3">120. On OTC meds</td><td colspan="3">121. Taking Herbal/CAM meds</td></tr>
</table>

Yes (1) No (2)	Yes (1) No (2) If yes: _____	Yes (1) No (2) If yes: _____
122. Taking ARV medication Yes (1) No (2) If yes: _____	**123. Other medication** (1) **Antacids:** Yes (1) No (2) (2) _____ (3) _____ (4) _____	**124. First line TB regimen initiated** **(1)** Rifampicin :_____mg **(2)** Isoniazid :_____ mg **(3)** Ethambutol :_____mg **(4)** Pyrazinamide :_____mg **(5)** Pyridoxine :_____ mg

PART D: CLINICAL ASSESMENT /LABORATORY / INVESTIGATIONS

125. Vital signs (1) BP: _____mmHg (2) Temp: _____oC (3) Pulse: _____ bpm (4) Resp: _____ bpm (5) **BODY WT:**_____ (6) Height: : _____	**126. Liver function tests** (1) ALT: _____ (2) AST: _____ (3) GGT: _____ (4) Albumin: _____ (5) Bilirubin: _____	**127. Renal function tests** (1) SCr: _____ (2) CrCl: _____ (3) BUN: _____ (4) Lactate: _____
125. HIV tests **(1)** Clinical stage: _____ **(2)** CD+4: _____ **(3)** VL: _____	**125. Complete blood count** (1) Hb: _____ g/dL (2) HCT: _____ % (3) PLT : _____ (4) WBC: _____	**127. WBC differentials** (1) Neutrophils _____ / _____% (2) Lymphocytes_____ / _____% (3) Monocyte _____ / _____% (4) Eosinophils _____ / _____% (5) Basophil _____ / _____%
127. Baseline sputum smear (1) +4: _____ (2) +3: _____ (3) +2: _____ (4) +1: _____	**128. Sputum conversion 8 week** (1) 4: _____ (2) +3: _____ (3) +2: _____ (4) +1: _____	**129. Sputum conversion 6 months** (1) 4: _____ (2) +3: _____ (3) +2: _____ (4) +1: _____

130: Antimycobacterial culture and sensitivity testing

(1) Rifampicin : (1) Sensitive (2) Not sensitive
(2) Isoniazid : (1) Sensitive (2) Not sensitive
(3) Ethambutol : (1) Sensitive (2) Not sensitive
(4) Pyrazinamide : (1) Sensitive (2) Not sensitive

PART E: TREATMENT OUTCOMES

After 2 months **(intensive phase**	**Successful outcome** (1) Cured (2) Completed treatment	**Poor outcome** (1) Died (2) Failure (3) Defaulted (4) Transferred out
After 6 months **(Continuation phase)**	**Successful outcome** (1) Cured (2) Completed treatment	**Poor outcome** (1) Died (2) Failure (3) Defaulted (4) Transferred out

APPENDIX C: Search strategy used for Chapter 7

	Key terms , synonyms and Boolean operators
1.	Pharmacokinetics.mp. /
2.	plasma concentration* /
3.	serum concentration*/
4.	Plasma level*/
5.	Serum level
6.	1 or 2 or 3 or 4 or 5
7.	Anti-tuberculosis.mp. or antituberculosis or antimycobacterial or anti-mycobacterial or tuberculosis drugs
8.	Rifampicin or rifampin or rifamycin
9.	Isoniazid
10.	Ethambutol
11.	Pyrazinamide
12.	7 or 8 or 9 or 10 or 11
13.	HIV or HIV/AIDS or AIDS
14.	Africa south of the Sahara or Central Africa or Africa or Sout Africa or North Africa
15.	(angola OR benin OR botswana OR burkina faso OR burundi OR cameroon OR cape verde OR central african republic OR chad OR comoros OR congo OR congo democratic republic OR djibouti OR equatorial guinea OR eritrea OR ethiopia OR gabon OR gambia OR ghana OR guinea OR guinea-bissau OR cote d'ivoire OR ivory coast OR kenya OR lesotho OR liberia OR madagascar OR malawi OR mali OR mozambique OR namibia OR niger OR nigeria OR (sao tome and principe) OR **rwanda** OR senegal OR seychelles OR sierra leone OR **somalia** OR south africa OR south sudan OR sudan OR swaziland OR tanzania OR togo OR uganda OR zambia OR zimbabwe).mp
16.	14 or 15
17.	12 and 16
18.	6 and 17
19.	13 and 18

APPENDIX D: Autocorrelation (acf) and partial autocorrelation (pacf) used to determine the appropriate model in Chapter 3

Table of the Durbin Watson statistic

Lag	Autocorrelation	D-W Statistic	*p*- value
1	0.19885238	1.5458292	0.068
2	-0.29003672	2.4952420	0.416
3	-0.54112113	2.9948506	0.010*
4	-0.25529368	2.2363960	0.254
5	0.23647951	1.2147494	0.396
6	0.05947071	1.4829648	0.760
7	0.13774206	1.1422718	0.754
8	0.02026473	1.2610609	0.740
9	0.02701049	0.9940092	0.818
10	0.05637657	0.8872469	0.782
11	-0.09351923	1.1390083	0.490
12	-0.09452253	0.8874547	0.810

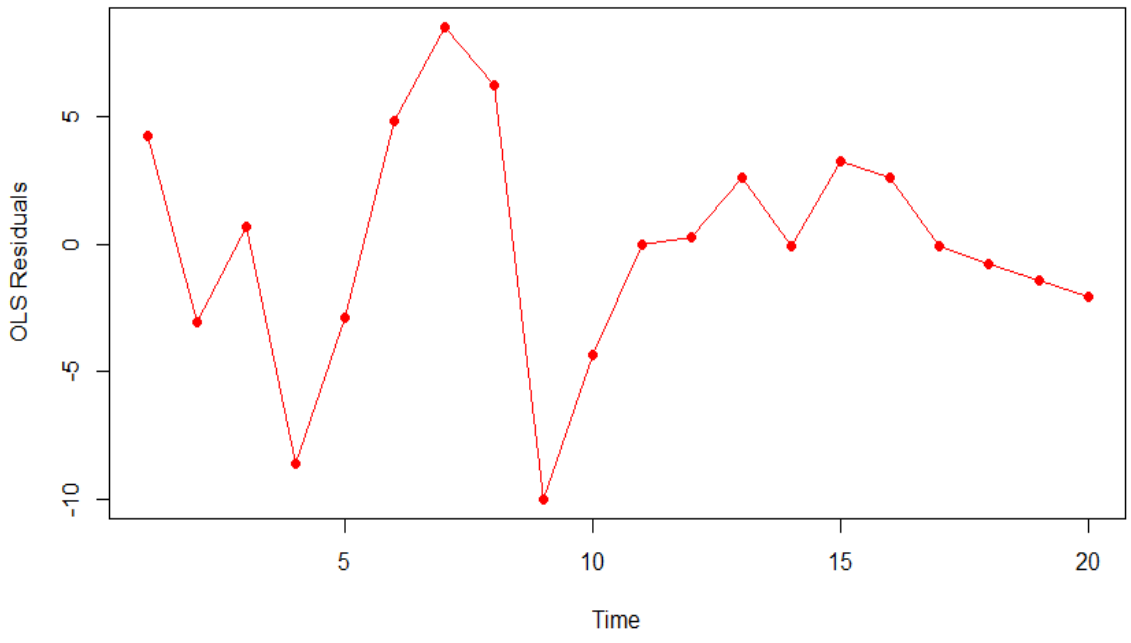
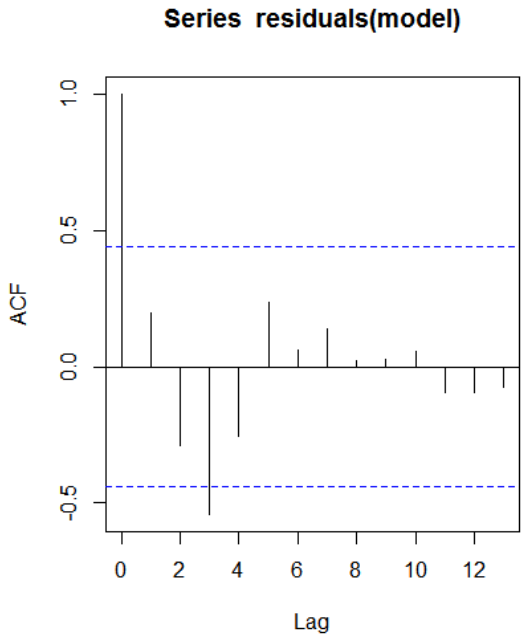
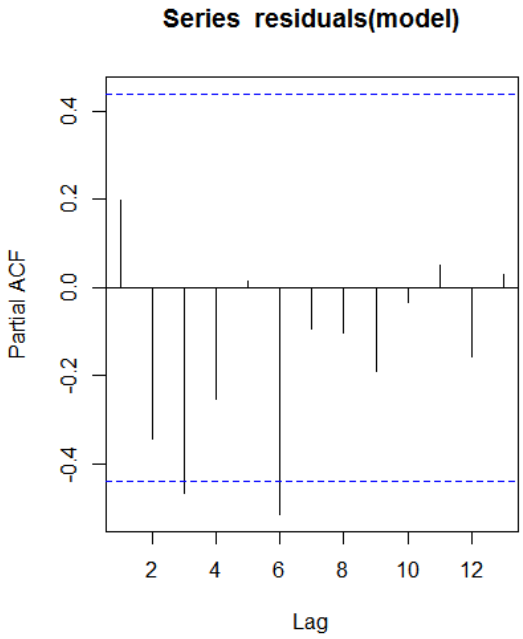


Figure 2: OLS residuals plot for treatment success for autocorrelations


Series residuals(model)
ACF
1.0
0.5
0.0
-0.5
0
2
4
6
8
10
12
Lag


Series residuals(model)
Partial ACF
0.4
0.2
0.0
-0.2
-0.4
2
4
6
8
10
12
Lag

APPENDIX E: R-codes for ITS analysis (Chapter 3)

Figure 1: Trends in the incidence rates of various types of tuberculosis

```
par(mar=c(5,4,4,4)+ 0.3)
plot(data$time,data$Allforms,ylim=c(0,16000), yaxt= "n", ylab="Absolute number of PTB, EPTB and DS-TB cases", xlab="Cohort", main="Absolute TB case notifications in Namibia", pch=19, xaxt="n", col="blue4", typ="o", cex=1.2, font.main=1)
axis(2, at=seq(0,16000,5000), col="black", las = 0, cex.axis= 1, labels=format(seq(0,16000,5000), big.mark= " ", format="d"))
lines(data$time,data$ptb,pch=0, xaxt="n", col="green4", typ="o", cex=1.2)
lines(data$time,data$eptb,pch=1, xaxt="n", col="green4", typ="o", cex=1.2)
abline(v=9.5,lty="dotted", lwd=2.5, col="black")
rect(9,0,10,18000,border=NA, col='#00000011')
text(18,13000,expression("DS-TB case"))
text(12,10000,expression("PTB cases"))
text(14,2000,expression("EPTB cases"))
 text(c(4,15),c(15000,15000),labels=c("Pre-CB-DOTS period","CB-DOTS period" ))
rect(2,14500, 6,15500, border=1)
rect(13,14500, 17,15500, border=1)
axis(1, at=1:20, labels= FALSE , tck= -0.02, cex.axis=1.2)
text(1:20, par("usr")[3] - 0.25, labels = data$cohort, srt=45, cex.axis=0.8, adj=1.5, xpd=TRUE)
 par(new = TRUE)
plot(data$time,data$mdr_coh, pch=15, ylim=c(0,1000),xlab = "", ylab = "", col="red3", axes=FALSE, type="b", lwd=1.5, cex=1.0)
lines(data$time,data$DRCases,pch=17, xaxt="n", col="red3", typ="o", cex=1.2)
text(16,350,expression("DR-TB cases"))
 text(18,160,expression("MDR-TB cases"))
mtext(" Absolute number of DR-TB and MDR-TB cases ", side=4, line=3)
> axis(4, ylim=c(0,600), col= "black", las = 2, cex.axis=1.0)
```

Figure 2: Trends in the

```
par(mar=c(5,4,4,4)+ 0.3)
plot(data$time,data$tsrall,ylim=c(0,100), ylab="Population covariates, %", xlab="Year of review of TB outcomes", pch=19, main= "Trends in TSR, CNR and population covariates", col="blue4", type="b", lwd=2.5, cex=1.5, xaxt="n", font.main =1)
lines(data$time,data$hivadt,pch=3, xaxt="n", col="purple", typ="o", bg="black", lwd=1.5, lty=4, cex=1)
lines(data$time,data$hivtb,pch=8, xaxt="n", col="purple", typ="o", bg="black", lwd=1.5, lty=4, cex=1)
lines(data$time,data$cbdotsper,pch=5, xaxt="n", col="green4", typ="o", bg="black", lwd=1.5, lty=4, cex=1)
 lines(data$time,data$artcov,pch=2, xaxt="n", col="green4", typ="o", bg="green4", lwd=1.5, lty=4, cex=1)
text(12,2,expression(MTP-I))
```

```
text(16,2,expression(MTP-II))
par (new = TRUE)
plot(data$time,data$cnr, pch=15, ylim=c(300,900), xlab = "", ylab = "",
col="deeppink1", axes=FALSE, type="b", lwd=2.5, cex=1.5)
mtext("-O- CNR/100 000", side=4, line=3)
axis(4, ylim=c(300,900), col= "black", las = 2, cex.axis=1.0)
axis(1, at=1:20, labels= FALSE , tck= -0.02, cex.axis=1.2)
text(1:20, par("usr")[3] - 0.25, las = 2, labels = data$cohort, srt=45, cex.axis=1, adj=1.5,
xpd=TRUE)
abline(v=9.5,lty="dotted", lwd=2.5, col="black")
abline(v=14.5,lty="dotted", lwd=1.5, col="black")
text(19,880,expression(paste("CB-DOTS coverage")))
text(18,790,expression(TSR))
text(19,700,expression(paste("ART coverage")))
text(18,600,expression(paste("TB-HIV coinfection")))
text(17,400,expression(paste("HIV prevalence")))
 text(18,520,expression(CNR))
text(12,900,expression("Post-intervention"))
text(3,900,expression("Pre-intervention"))
```

Figure 3b

```
par(mfrow=c(2,2))
plot(data$time, data$tsrall, ylab="Treatment success rates, %", xlab="Year of review of
TB outcomes", ylim=c(0,100),pch=23,xaxt="n", col="black", bg="blue4",font.main=1)
title(main=expression(paste(bold("A) "), " Treatment success: DS-TB")), font.main=1)
axis(1, at=1:20, labels= FALSE , tck= -0.02, cex.axis=1.2)
text(1:20, par("usr")[3] - 0.25, las = 2, labels = data$cohort, srt=45, cex.axis=1, adj=1.5,
xpd=TRUE)
lines(data$time[1:8], fitted(c)[1:8],col="blue4", lwd=2.5)
lines(data$time[10:20], fitted(c)[10:20],col="blue4", lwd=2.5)
segments(10,c$coef[1] + c$coef[2]*10,20,c$coef[1] +
c$coef[2]*20,lty=2,lwd=2.5,col="blue4")
abline(v=9.5,lty="dotted", lwd=2.5, col="blue4")
rect(8.5,0,10,100,border=NA, col='#00000011')
lines(data$time[1:8], fitted(r)[1:8],col="green4", lwd=2.5, lty=3)
lines(data$time[10:20], fitted(r)[10:20],col="green4", lwd=2.5, lty=3)
lines(data$time[1:8], fitted(p)[1:8],col="deeppink1", lwd=2, lty=6)
lines(data$time[10:20], fitted(p)[10:20],col="deeppink1", lwd=2, lty=6)
points(data$time, data$curedall, ylim=c(0,100),pch=20,xaxt="n", col="green4",
bg="green4")
points(data$time, data$completeall, ylim=c(0,100),pch=10,xaxt="n", col="deeppink1",
bg="deeppink")
text(18,95,expression(TSR))
text(13,50,expression(Completed))
text(13,30,expression(Cured))
```

```
text(c(5,15),c(5,5),labels=c("Pre-CB-DOTS period","Post CB-DOTS period (MTP-I and II)"))
```

Figure 3b

```
plot(data$time[12:19], data$mdrTSR[12:19], ylab="Treatment success rates, %", xlab="Year of review of TB outcomes", ylim=c(0,100),pch=23,xaxt="n", col="blue4", bg="blue4", font.main=1)
title(main=expression(paste(bold("B) "), "Treatment success: DR-TB")), font.main=1)
abline(lm(data$mdrTSR[12:19] ~ data$time[12:19], data=data[12:19]), col="blue4")
points(data$time[12:19], data$xdrTSR[12:19], ylim=c(0,100),pch=1,xaxt="n", col="purple", bg="purple", cex=1)
abline(lm(data$xdrTSR[12:19] ~ data$time[12:19], data=data[19:20]), col="purple")
text(16,75,expression("TSR for MDR-TB cases"))
text(16,20,expression("TSR for XDR-TB cases"))
axis(1, at=12:19, labels= FALSE , tck= -0.02)
text(12:19, par("usr")[3] - 0.25, las = 2, labels = data$cohort[12:19], srt=45, cex.axis=1, adj=1.2, xpd=TRUE)
text(14,90,expression(paste("Post CB-DOTS period (MTP-I and II)")))
```

Figure 3c

```
plot (data$time, data$ptbtsr, ylab="Treatment success rates, %", xlab="Year of review of TB outcomes", ylim=c(0,100),pch=23,xaxt="n", col="blue4", bg="blue4", font.main=1)
title(main=expression(paste(bold("C) "),"Treatment success: PTB")), font.main=1)
lines(data$time[1:9], fitted(ptbtsr)[1:9],col="blue4", lwd=2.5)
lines(data$time[10:20], fitted(ptbtsr)[10:20],col="blue4", lwd=2.5)
segments(10, ptbtsr$coef[1] + ptbtsr$coef[2]*10,20, ptbtsr$coef[1] + ptbtsr$coef[2]*20,lty=2,lwd=2.5,col="blue4")
abline(v=9.5,lty="dotted", lwd=2.5, col="black")
rect(9,0,10,100,border=NA, col='#00000011')
lines(data$time[1:9], fitted(ptbcure)[1:9],col="green4", lwd=2.5, lty=3)
lines(data$time[10:20], fitted(ptbcure)[10:20],col="green4", lwd=2.5, lty=3)
points(data$time, data$ptbcure, ylim=c(0,100),pch=20,xaxt="n", col="green4", bg="green4")
lines(data$time[1:9], fitted(ptbcompleted)[1:9],col="deeppink1", lwd=2.5, lty=6)
lines(data$time[10:20], fitted(ptbcompleted)[10:20],col="deeppink1", lwd=2.5, lty=6)
points(data$time, data$ptbcomplete, ylim=c(0,100),pch=10,xaxt="n", col="deeppink1", bg="deeppink1")
axis(1, at=1:20, labels= FALSE , tck= -0.02)
text(1:20, par("usr")[3] - 0.25, las = 2, labels = data$cohort, srt=45, cex.axis=1, adj=1.2, xpd=TRUE)
text(15,92,expression("TSR for PTB cases"))
text(15,60,expression("Cure rates for PTB"))
text(15,35,expression("Completion rates for PTB"))
```

```
text(c(5,15),c(4,4),labels=c("Pre-CB-DOTS period","Post CB-DOTS period (MTP-I and II)"))
```

Figure 3d

```
plot(data$time, data$etbcompleted, ylab="Treatment success rate, %", xlab="Year of review of TB outcomes", ylim=c(0,100),pch=23,xaxt="n", col="deeppink1", bg="deeppink1", font.main=1)
title(main=expression(paste(bold("D) "),"Treatment success: EPTB")), font.main=1)
lines(data$time[1:9], fitted(etb1)[1:9],col="deeppink", lwd=2.5)
lines(data$time[10:20], fitted(etb)[10:20],col="deeppink1", lwd=2.5)
segments(10,etb$coef[1] + etb$coef[2]*10,20,etb$coef[1] + etb$coef[2]*20,lty=2,lwd=2.5,col="deeppink1")
axis(1, at=1:20, labels= FALSE , tck= -0.02)
text(1:20, par("usr")[3] - 0.25, las = 2, labels = data$cohort, srt=45, cex.axis=1, adj=1.2, xpd=TRUE)
abline(v=9.5,lty="dotted", lwd=2.5, col="black")
rect(9,0,10,100,border=NA, col='#00000011')
text(15,90,expression("EPTB completion rate"))
text(c(5,15),c(4,4),labels=c("Pre-CB-DOTS period","Post CB-DOTS period (MTP-I and II)"))
```

Figure 4a

```
par(mfrow=c(2,2))
plot(data$time, data$ptbtsr, ylab="Treatment success rates, %", xlab="Year of review of TB outcomes", ylim=c(0,100),pch=23,xaxt="n", col="blue4", bg="blue4", font.main=1)

title(main=expression(paste(bold("A) "),"Treatment success: All pulmonary tuberculosis cases")), font.main=1)

lines(data$time[1:9], fitted(ptbtsr)[1:9],col="blue4", lwd=2.5)

lines(data$time[10:20], fitted(ptbtsr)[10:20],col="blue4", lwd=2.5)

segments(10, ptbtsr$coef[1] + ptbtsr$coef[2]*10,20, ptbtsr$coef[1] + ptbtsr$coef[2]*20,lty=2,lwd=2.5,col="blue4")
abline(v=9.5,lty="dotted", lwd=2.5, col="black")
rect(9,0,10,100,border=NA, col='#00000011')
lines(data$time[1:9], fitted(ptbcure)[1:9],col="green4", lwd=2.5, lty=3)
lines(data$time[10:20], fitted(ptbcure)[10:20],col="green4", lwd=2.5, lty=3)
points(data$time, data$ptbcure, ylim=c(0,100),pch=20,xaxt="n", col="green4", bg="green4")
lines(data$time[1:9], fitted(ptbcompleted)[1:9],col="deeppink1", lwd=2.5, lty=6)
lines(data$time[10:20], fitted(ptbcompleted)[10:20],col="deeppink1", lwd=2.5, lty=6)
points(data$time, data$ptbcomplete, ylim=c(0,100),pch=10,xaxt="n", col="deeppink1", bg="deeppink1")
axis(1, at=1:20, labels= FALSE , tck= -0.02, cex.axis=1.2)
```

```
text(1:20, par("usr")[3] - 0.25, las = 2, labels = data$cohort, srt=45, cex.axis=1, adj=1.5, xpd=TRUE)
text(15,92,expression("TSR for PTB"))
text(15,60,expression("Cure rates for PTB"))
text(15,35,expression("Completion rates for PTB"))
text(c(5,15),c(4,4),labels=c("Pre-CB-DOTS period","Post CB-DOTS period (MTP-I and II)"))
```

Figure 4b

```
plot(data$time, data$nsptsr, ylab="Treatment outcomes, %", xlab="Year of review of TB outcomes", ylim=c(0,100),pch=23,xaxt="n", col="blue4", bg="blue4", font.main=1)

title(main=expression(paste(bold("B) "),"New smear-positive PTB")), font.main=1)

lines(data$time[1:9], fitted(nsp1g)[1:9],col="blue4", lwd=2.5)
lines(data$time[10:20], fitted(nsp1g)[10:20],col="blue4", lwd=2.5)
segments(10,nsp1g$coef[1] + nsp1g$coef[2]*10,20,nsp1g$coef[1] + nsp1g$coef[2]*20,lty=2,lwd=2.5,col="blue4")
abline(v=9.5,lty="dotted", lwd=2.5, col="black")
rect(9,0,10,100,border=NA, col='#00000011')
lines(data$time[1:9], fitted(nsp2g)[1:9],col="green4", lwd=2.5, lty=3)
lines(data$time[10:20], fitted(nsp2g)[10:20],col="green4", lwd=2.5, lty=3)
lines(data$time[1:9], fitted(nsp3g)[1:9],col="deeppink", lwd=2.5, lty=6)
lines(data$time[10:20], fitted(nsp3g)[10:20],col="deeppink", lwd=2.5, lty=6)
points(data$time, data$nspcured, ylim=c(0,100),pch=20,xaxt="n", col="green4", bg="green4")
points(data$time, data$nspcompleted, ylim=c(0,100),pch=10,xaxt="n", col="deeppink", bg="deeppink")
text(18,92,expression(TSR))
text(13,65,expression("Cure rate"))
text(13,16,expression("Completion rate"))
text(c(5,15),c(4,4),labels=c("Pre-CB-DOTS period","Post CB-DOTS period (MTP-I and II)"))
axis(1, at=1:20, labels= FALSE , tck= -0.02)
text(1:20, par("usr")[3] - 0.25, las = 2, labels = data$cohort, srt=45, cex.axis=1, adj=1.2, xpd=TRUE)
```

Figure 4c

```
plot(data$time, data$retsr, ylab="Treatment outcomes, %", xlab="Year of review of TB outcomes", ylim=c(0,100),pch=23,xaxt="n", col="blue4", bg="blue4")
title(main=expression(paste(bold("C) "),"Retreatment smear-positive PTB")), font.main=1)

lines(data$time[1:9], fitted(ret1g)[1:9],col="blue4", lwd=2.5)
```

```
lines(data$time[10:20], fitted(ret1g)[10:20],col="blue4", lwd=2.5)
segments(10,ret1g$coef[1] + ret1g$coef[2]*10,20,ret1g$coef[1] + ret1g$coef[2]*20,lty=2,lwd=2.5,col="blue4")
abline(v=9.5,lty="dotted", lwd=2.5, col="black")
axis(1, at=1:20, labels= FALSE , tck= -0.02)
text(1:20, par("usr")[3] - 0.25, las = 2, labels = data$cohort, srt=45, cex.axis=1, adj=1.2, xpd=TRUE)
lines(data$time[1:9], fitted(ret2g)[1:9],col="green4", lwd=2.5, lty=3)
lines(data$time[10:20], fitted(ret2g)[10:20],col="green4", lwd=2.5, lty=3)
lines(data$time[1:9], fitted(ret3g)[1:9],col="deeppink1", lwd=2.5, lty=6)
lines(data$time[10:20], fitted(ret3g)[10:20],col="deeppink1", lwd=2.5, lty=6)
points(data$time, data$recured, ylim=c(0,100),pch=20,xaxt="n", col="green4", bg="green4")
points(data$time, data$recompleted, ylim=c(0,100),pch=10,xaxt="n", col="deeppink1", bg="deeppink1")
text(18,83,expression(TSR))
text(13,42,expression("Cure rate"))
text(13,24,expression("Completion rate"))
text(c(5,15),c(4,4),labels=c("Pre-CB-DOTS period","Post CB-DOTS period (MTP-I and II)"))
abline(v=9.5,lty="dotted", lwd=2.5, col="black")
rect(9,0,10,100,border=NA, col='#00000011')
```

Figure 4d

```
plot(data$time, data$sncompleted, ylab="Treatment outcomes, %", xlab="Year of review of TB outcomes", ylim=c(0,100),pch=23,xaxt="n", col="deeppink", bg="deeppink", font.main=1)
title(main=expression(paste(bold("D) "),"Smear-negative PTB")), font.main=1)
lines(data$time[1:9], fitted(sn1g)[1:9],col="deeppink", lwd=2.5)
lines(data$time[10:20], fitted(sn1g)[10:20],col="deeppink", lwd=2.5)
segments(10,sn1g$coef[1] + sn1g$coef[2]*10,20,sn1g$coef[1] + sn1g$coef[2]*20,lty=2,lwd=2.5,col="deeppink")
axis(1, at=1:20, labels= FALSE , tck= -0.02)
text(1:20, par("usr")[3] - 0.25, las = 2, labels = data$cohort, srt=45, cex.axis=1, adj=1.2, xpd=TRUE)
abline(v=9.5,lty="dotted", lwd=2.5, col="black")
rect(9,0,10,100,border=NA, col='#00000011')
text(18,65,expression("Completion rate"))
text(c(5,15),c(4,4),labels=c("Pre-CB-DOTS period","Post CB-DOTS period (MTP-I and II)")
```

APPENDIX F: Ethical Approval from University of Namibia

UNAM
UNIVERSITY OF NAMIBIA

STUDENT ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: SOM/114/2016 **Date: 16 August, 2016**

This Ethical Clearance Certificate is issued by the University of Namibia Research Ethics Committee (UREC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the Faculty/Centre/Campus Research & Publications Committee sitting with the Postgraduate Studies Committee.

Title of Project: PREVALENCE, DETERMINANTS AND OUTCOMES OF SUB-THERAPEUTIC SERUM LEVELS OF FIRST LINE ANTI-TUBERCULOSIS MEDICINES AMONG PATIENTS IN NAMIBIA

Nature/Level of Project: DOCTORATE

Principal Researcher: DAN KIBUULE

Student Number : 201501352

Host Department & Faculty: School of Medicine
Main Supervisor : Prof. R. Verbeeck (Main) Prof. T. Rennie; Prof. E. Ene (Co)

Take note of the following:

(a) Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the UREC. An application to make amendments may be necessary.
(b) Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the UREC.
(c) The Principal Researcher must report issues of ethical compliance to the UREC (through the Chairperson of the Faculty/Centre/Campus Research & Publications Committee) at the end of the Project or as may be requested by UREC.
(d) The UREC retains the right to:
  (i). withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,
  (ii). request for an ethical compliance report at any point during the course of the research.

UREC wishes you the best in your research.

Dr. H. M. Kapenda
Director: Centre for Research and Publications
ON BEHALF OF UREC

APPENDIX G: Ethical approval Ministry of Health And Social Services

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198	Ministerial Building	Tel: 061 – 203 2562
Windhoek	Harvey Street	Fax: 061 – 222558
Namibia	Windhoek	E-mail: hnangombe@gmail.com

OFFICE OF THE PERMANENT SECRETARY

Ref: 17/3/3
Enquiries: Ms. H. Nangombe

Date: 13 October 2016

Mr Dan Kibuule
School of Pharmacy
University of Namibia
Windhoek
Namibia

Dear Mr Kibuule

Re: Prevalence, Determinants and Outcomes of Sub-Therapeutic serum levels of first line Anti-Tuberculosis medicines among patients in Namibia

1. Reference is made to your application to conduct the above-mentioned study.

2. The proposal has been evaluated and found to have merit.

3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;

3.2 No other data should be collected other than the data stated in the proposal;

3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;

3.4 A quarterly report to be submitted to the Ministry's Research Unit;

3.5 Preliminary findings to be submitted upon completion of the study;

3.6 Final report to be submitted upon completion of the study;

3.7 Separate permission should be sought from the Ministry for the publication of the findings.

Yours sincerely,

14 OCT 2015

Andreas Mwoombola (Dr)
Permanent Secretary

APPENDIX H: Ethical approval Khomas Region

9-0/0001

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13322
Windhoek
Namibia

Khomas Region Directorate
Florence Nightingale Street
Windhoek

Tel: 061 - 2035011
Fax: 061 – 235997

Enq: Mr. B. Isaacs | Ref: S4/9 | Date: 28 November 2018

OFFICE OF THE DIRECTOR

STAFF MATTER: CONFIDENTIAL

MR. DAN KIBUULE
SCHOOL OF PHARMACY
WINDHOEK
NAMIBIA

Dear Mr. Kibuule

I have pleasure to inform you that permission as per Permanent Secretary's approval has been granted for you to conduct a study on " Prevalence Determinants and Outcomes of Sub-Therapeutic serum levels of first line Anti-Tuberculosis medicines among patients in Namibia." Katutura Health Centre for a period of two (2) weeks from the 29 November until 12 December 2018.

The office wishes you success with your research.

Yours sincerely

MINISTRY OF HEALTH AND SOCIAL SERVICES
DIRECTOR
29 NOV 2018
WINDHOEK

MS. ELIZABETH MUREMI
DIRECTOR: KHOMAS REGION

"Your Health, Our Concern"

APPENDIX I: Ethical approval Katutura Intermediate Hospital

Republic of Namibia

Ministry of Health and Social Services

Private Bag 13215
203 4004/5
WINDHOEK
222706
Namibia

Intermediate Hospital Katutura
Independence Avenue
WINDHOEK

Telephone (061)
Telefax (061)

Enquiries: Ms. F.M. Shiweda

Date: 01 November 2017

OFFICE OF THE CHIEF MEDICAL OFFICER

Mr. Dan Kibuule
School of Pharmacy
University of Namibia
Windhoek, Namibia

Dear Mr. Dan Kibuule

RE: PREVALENCE, DETERMINANTS AND OUTCOMES OF SUB-THERAPEUTIC SERUM LEVELS OF FIRST LINE ANTI-TUBERCULOSIS MEDICINES AMONGST PATIENTS IN NAMIBIA.

The above mentioned subject refers:

This office hereby grants you permission to do research on prevalence, determinants and outcomes of sub-therapeutic serum levels of first line anti-Tuberculosis medicine amongst patients in Namibia, Intermediate Hospital Katutura, Khomas Region, MoHSS.

Thank you

Yours in health

02/Nov/17

DR. F. M. SHIWEDA
CHIEF MEDICAL OFFICER

MINISTRY OF HEALTH AND SOCIAL SERVICES
PRIVATE BAG 13215
WINDHOEK NAMIBIA
02 -11- 2017
INTERMEDIATE HOSPITAL KATUTURA

APPENDIX J: Optimizing treatment outcome of first-line anti-tuberculosis drugs: the role of therapeutic drug monitoring. European Journal of Clinical pharmacology. 2016 Aug. 1; 72(8):905-16.