Original Research

Predictors of tuberculosis treatment success under the DOTS program in Namibia

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Abstract

Objectives: 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%. Consequently, the objective of this study was to ascertain the predictors of treatment success rates under DOTS in Namibia to provide future direction.

Methods: A nation-wide comparative analysis of predictors of treatment success was undertaken. Tuberculosis cases in the 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: 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 as were: Region of DOTS implementation (p=0.001), type of DOT supporter (p<0.001), sputum conversion at 2 months (p=0.013), DOT regimen (p<0.001), cotrimoxazole prophylaxis (p=0.002) and HIV co-infection (p=0.001).

Conclusion: Targeted programmatic, clinical and treatment interventions are required to enhance DOTS treatment success in Namibia. These are now ongoing.

1. 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 approximately 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 World Health Organisation (WHO) and the United Nations 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 (LMICs) 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]. TSR are even lower among the retreatment and smear negative cases[13,18]. Consequently, these sub-optimal treatment success rates are 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 including pharmacokinetic variability , socio-demographics 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 LMICs where the burden of TB remains high[9]. In view of this, the objective of this study was to ascertain the predictors of treatment success rates under DOTS in Namibia to provide future direction

2. Methods
2.1 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.

In Namibia, high quality DOTS services that include DOT are accessible at all public health facilities, i.e. facility based DOT (FB-DOTS) or in all communities, i.e. community based DOT (CB-DOTS) in all the14 geographical regions of Namibia. The FB-DOTS services can be accessed across all levels of care. These include 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 CB-DOTS workers that include DOT supervisors, DOT Nurses and

DOT supporters who directly observe TB treatment. They also include health facility nurses, work-place peers, and community based workers as well as guardians (family/neighbor/relative) and any others preferred by the patient.

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.

2.2 Tuberculosis DOTS program in Namibia

In Namibia, TB is managed using the WHO DOTS at health facilities (FB-DOTS) and at the community level (CB-DOTS) implemented by NTLP. Namibia achieved a country-wide DOTS coverage at all public health facilities, that is 42 hospitals, 34 health centers and 244 clinics, by 1996. Nonetheless, in 2004 the country reported the highest case notification rate, lowest TSR for tuberculosis as well as the emergence of drug resistant TB (DR-TB). Consequently in 2004, a CB-DOTS strategy was designed to improve TSR from 65% to 85% by 2009 and to 90% by 2015, among other TB indicators under the first and second medium term plans (MTP-I, 2004-2009; MTP-II, 2010-2015) for Tuberculosis and Leprosy. CB-DOTS was implemented in all districts in partnership with NTLP and community-based HIV/TB organizations (CBOs), paving the way for standardized regimens, which were Fixed-Dose Combination (FDC) drugs for first-line tuberculosis treatment, the revision of national guidelines for case management of tuberculosis and the ETR to report treatment outcomes. The diagnosis of TB was by microscopy (i.e. positive sputum smear or culture) and/or clinical signs. The FDC regimens for drug susceptible TB (DST) for new adult, new pediatric and retreatment cases were 2RHZE/4RHE, 2RHZ/4RH and 1RHZE/2RHZE/5RHE respectively. A team of community-based persons comprising of CHW (community healthcare workers), i.e. CB-DOT supervisors and FB-DOT supervisors and DOT nurses, DOT field promoters, and CB-DOT supporters implemented the CB-DOTS programme at each health district unit. The DOT-supporters such as family/relatives or workplace peers or CHWs directly observe the administration of the TB-medication at community DOT points, households and workplaces. In addition, the quality of CB-DOTS was enhanced through (i) the scale up quality assured bacteriology laboratories, up from 30 (1 lab per 67,000 people) in 2004 to 36 in 2015 to increase case detection, (ii) the production of a CB-DOTS training manual and the WHO guideline for TB treatment supporters to standardize treatment with supervision and

patient support, (iii) a system for effective supply and management of TB drugs as well as (iv) a monitoring and evaluation system for effective measurement.

2.3 Data and statistical analysis

The main outcome of the study is the treatment success, which 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]. Treatment success for extra pulmonary tuberculosis (EPTB) in Namibia is mainly determined by treatment completion and/or negative microscopy and biopsy results. An unsuccessful outcome in this study referred to TB cases recorded as loss-to-follow-up (LTFU), transferred out, failed treatment or died. Cases of DR-TB are hospitalized and managed according to the treatment guidelines for DR-TB, which comprise at least five second line anti-tuberculosis medicines. These include levofloxacin, PASA, ethionamide, kanamycin, pyrazinamide, clofazimine, and capreomycin for 12-18 months of treatment.

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 ETR by the principal research team.

Data were retrospectively abstracted over 10-year review period (2004/Q3 and 2016/Q1), which coincides with the scale-up to high quality CB-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 undertaken 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 the NIP are subsequently validated by the facility, district and regional TB care teams. Data on treatment outcomes and covariates were exported to RStudio software for statistical analysis. 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=0.05.

2.4 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). 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.

3. Results

During the study period (2004/ Q3–2016/Q1), out of the 104,604 TB cases registered, 1 was excluded due to missing data on outcome and covariates (Figure 1). 27747 patients had an outcome recorded as unavailable and were excluded from the bivariate and multivariate analysis and 2974 cases eventually met the criteria for multivariate analysis for all covariates and were entered in the model (Figure 1).

Figure 1 – Flow chart for inclusion criteria of TB cases
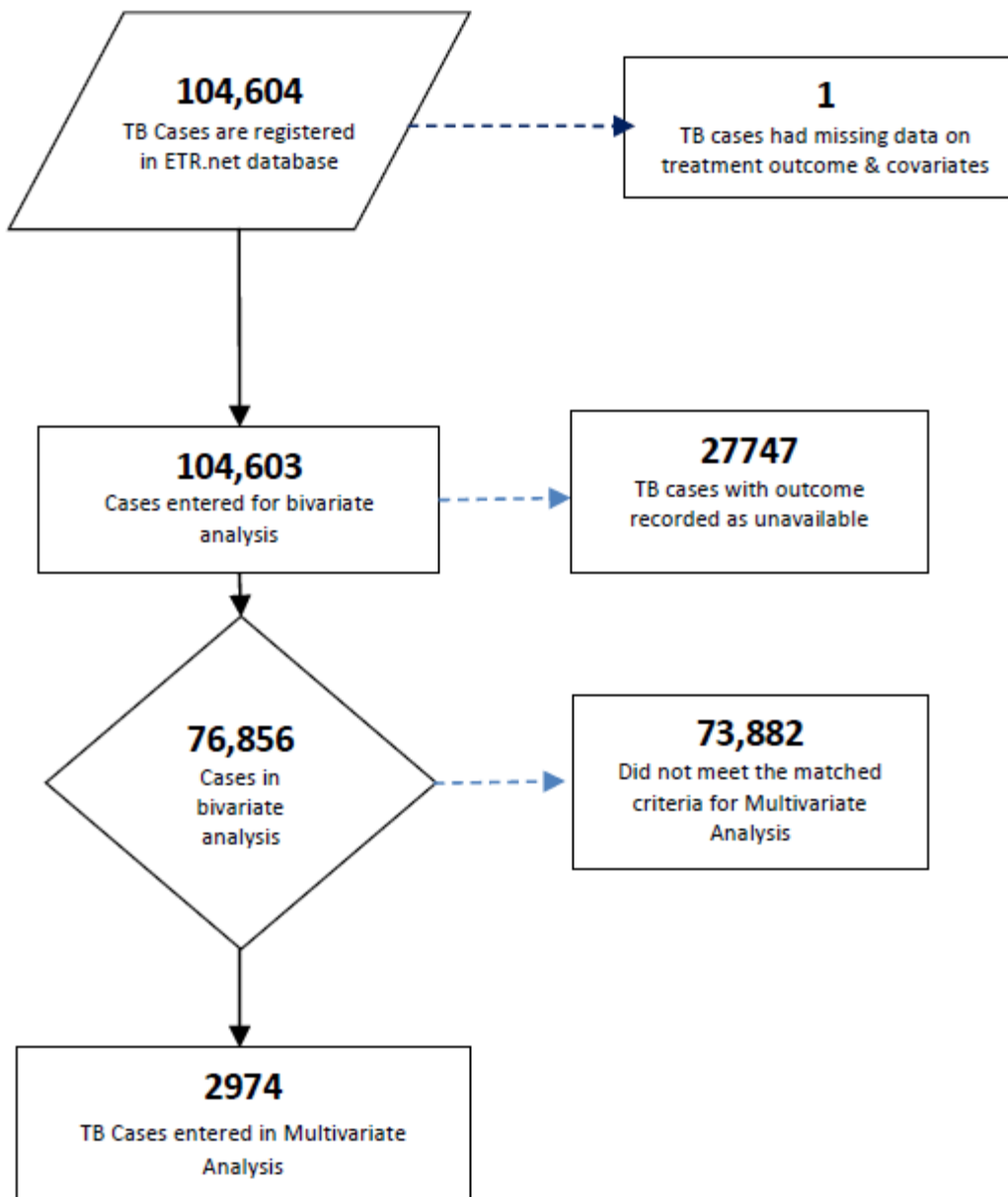
Overall, a total 104,603 TB cases were registered at 300 DOTS sites in 37 districts in all 14 regions of Namibia. This gives an average of 2,226 (range: 1500 – 3500) cases registered every quarter. The majority of the cases were registered at primary health care facilities (78.9%), predominantly at health centers (62.8%) (Table 1).

Table 1: Univariate analysis of covariates with treatment outcome (n=76,856)

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 (0.30)			
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, * = significant p value by Pearson Chi-Square, MTP = medium term plans, TB= Tuberculosis, EPTB = extra pulmonary tuberculosis, PTB = pulmonary tuberculosis, IPT= Isoniazid Prophylaxis Therapy, CPT=cotrimoxazole prophylaxis, MDR-TB = drug resistant tuberculosis*

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, Supplement A). Most of the cases were male (57.9%), aged between 25-44 years (52.6%) and about half were co-infected with HIV (47.9%), which is seen as high, with HIV positive

patients appreciably more likely to have treatment failure (p<0.000). This was also seen in the multivariate analysis (Table 2). However, no difference if HIV patients are on HAART (p=0.127) (Table 1).

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 TB (PTB, 80.8%) compared to 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.

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 2). Death and LTFU were the most prevalent unsuccessful treatment outcomes (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), no region achieved the 90% global target for TSR. Only two regions out of 14, Zambezi and Omaheke, surpassed the 85% WHO TSR targets (Figure 3).

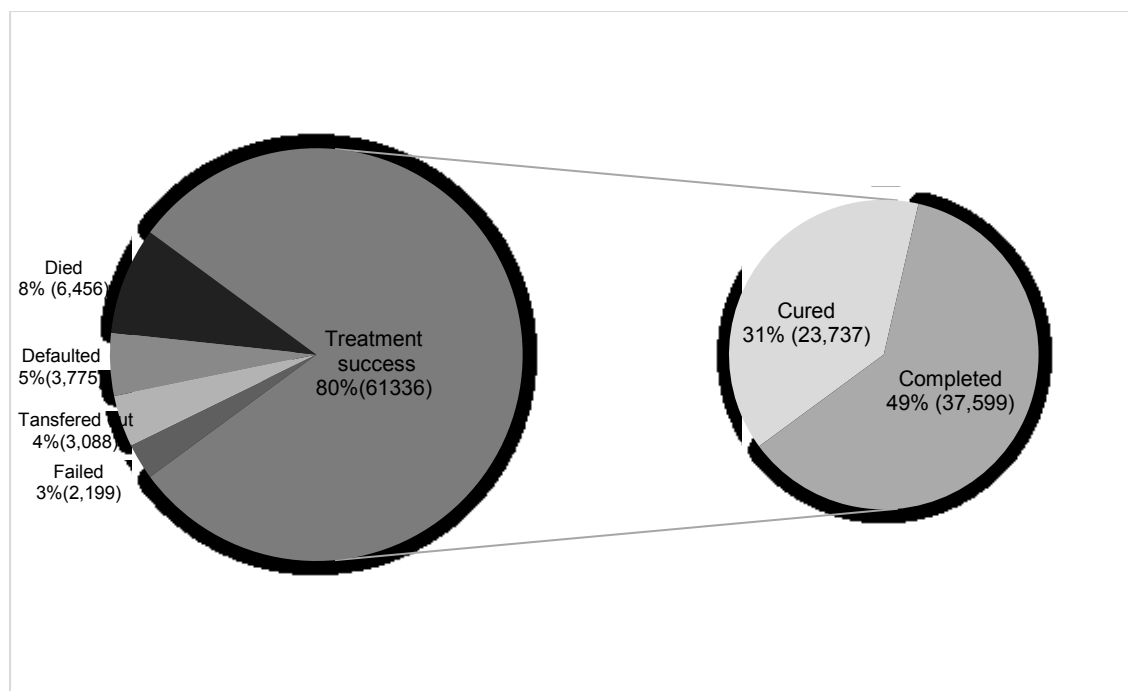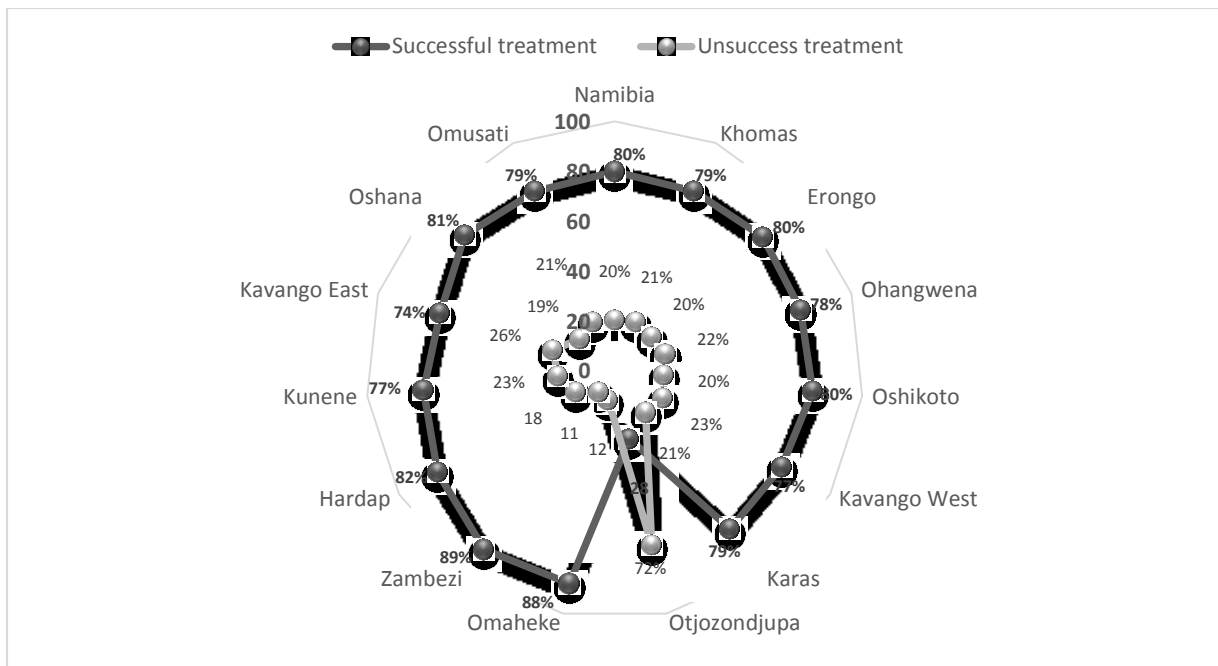**Figure 2: Categories of treatment outcomes (n=76856, not evaluated = 27747)**

Figure 3: Period prevalence of TB Treatment outcomes by regions in Namibia

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).

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 (χ^2 = 11.9, *p*=0.156 with *df* = 8).

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			1	
Facility level	1.7	2		0.428
Hospital	1.1	1	1.4(0.8, 2.4)	0.287
PHC Clinic	1.6	1	1.3(0.9, 2.0)	0.211
Health Center			1	
Patients sex				
Male	1.7	1	0.8(0.6,1.1)	0.197
Female			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+				
Previously registered				
No	0.1	1	0.6(0.0,9.0)	0.726
Yes			1	
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			1	
Pulmonary	0.0	5	0.0(0.0,1.0)	1.000
Lymph Nodes	0.0	1	1.3	0.999
Miliary	0.0	1	0.4	1.000
Other Sites	0.0	1	0.4	1.000
Pleura	0.0	1	0.0	1.000
Bones/Joints	0.0	1		0.999
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	
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)	0.999
2 HRZ / 4 HR	0.0	1	1	
Smear non conversion	459.1	1	0.02(0.01,0.03)	0.000*
Yes			1	
No				
Sputum conversion 2 months	8.7	2	0.7(0.5,1.1)	0.013*
Converted to smear negative	2.8	1	0.5(0.3,0.8)	0.092
Remaining smear positive	7.9	1	1	0.005
Defaulted+Died+Transfered+Not available				

	Wald	df	OR(CI)	p-value
Antiretroviral Treatment	0.8	1	0.8(0.6,1.2)	0.363
No			1	
Yes				
Cotrimoxazole Prophylaxis	9.6	1	0.4(0.2,0.7)	0.002*
No			1	
Yes				
IPT (isoniazid) exposure				
No	0.5	1	1.2(0.7,2.6)	0.464
Yes			1	
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			1	
Constant	0.000	1	0.121	1.000

a. Variable(s) entered on step 1: Medium Term Plan strategic plan, I or II, REGION, FACLEVEL, PREVREGT, SEX, REGIMENTYPE, DIAGCLASS, SITEINFECTEDTB, MDRPatientt, DOTTYPE, PtAgegroup, NOTCONVERTED, SPUTUM2mon, ARTtreat, CPTtherapy, IPTrecieved, HIVSTATUS.

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 ($p<0.001$) – with some regions such as Otjiwarongo (OR=2.8, 95%CI:1.3,6.4) having significantly higher TSR than others, 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 (CPT - OR=0.4, 95%CI: 0.2, 0.7).

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, cotrimoxazole prophylaxis and sputum conversion at 2 months were identified as independent risk factors for successful treatment outcomes for first line regimens (Table 2).

4. Discussion

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

These findings are consistent with the WHO global tuberculosis reports on in LMIC and 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 (Figure 2). Previous studies in the Omaheke region in Namibia, and in other LMICs such as Uganda and South Africa, suggest that low acceptance and poor implementation of CB-DOTS are due to social, cultural, programmatic factors [21,30]. These factors together with access to DOTS services[31] are 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 a significant association between TB treatment success and all programmatic, patient demographics 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 in South Africa and Uganda[25,26] have also associated poor treatment outcomes to the male gender, HIV co-infection, diagnostic and the sputum conversion at 2 months as well as the WHO TB regimen used[33]. In addition, coinfection with HIV and/or diabetes among TB patients, patient related demographic characteristics[34,35], and pharmacokinetic variability among populations[36]. In addition in this study, 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 be due to the inappropriate choice of TB regimens[37,38], 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 the region, were significant predictors of TB treatment outcomes (Table 2). Our findings though differ from other studies that found that patient's demographics including their age[41,46] and male-gender[27,46-49], as well as the 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 to studies by Nakiyingi et al. and others 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 the importance of optimizing the TB regimens[36,41,50], strengthening the support DOTS support system and instigating a system to screen and monitor for risk for poor treatment outcomes among patients with HIV co-infection, and prior exposure to cotrimoxazole, to maximize the outcome of DOTS. The regional variation in TSR may be due population related characteristics and/or access and 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]. The objective being to make appropriate dosage adjustments to improve outcomes. Several studies have shown that up to 75% of the patients do not achieve optimal drug levels and adjustments of doses will improve outcomes.

Our findings are also different from a number of other studies that show favourable treatment outcomes among patients on ART and IPT and CPT. These differences may be due to the fact that our study was of a retrospective design that utilized national 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 including possible adverse drug reactions and the type of ART regimen. We will be undertaking a separate study to investigate the side-effects of treatment regimens as well as undertaking a separate analysis of MDR-TB cases. However, the study gives a true reflection of current routine clinical practice in Namibia for

these patients and describes the limitations of the current DOTS interventions using national 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 outcomes among patients at risk of poor outcomes, which Namibia is already starting to review in its third strategic plan.

Author contributions

DK, RKV, RN, FM, AT, AA, GG, EE and TR help devise the study; DK, GG and EE undertook the data collection and initial analysis; DK, RKV, BBG and TR produced the first manuscript. All authors contributed to successive drafts as well as the update. All authors approved the final paper.

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Supplement A: **National Strategic Plan on Tuberculosis (MTP-I and MTP-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 firstline 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 program (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*