**Original Research**

**Predictors of tuberculosis treatment success under the DOTS program in Namibia**

Dan Kibuule1, Roger K Verbeeck1, Ruswa Nunurai2, Farai Mavungha 2, Albertina Thomas2, Amutenya Amutenya2, Guna Gunther3, Ette Ene4, Brian Godman5,6,7,8, Timonthy Rennie1

1School of Pharmacy, Faculty of Health Sciences, University of Namibia, Windhoek, Namibia

2National Tuberculosis and Leprosy Programme, Ministry of Health and Social Services, Windhoek, Namibia

3Tuberculosis Clinic, Ministry of Health and Social Services, Intermediate Hospital: Katurua, Windhoek, Namibia

4Anoixis Corporation, Natick, MA, USA

5Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

**6**Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

7Health Economics Centre, Liverpool University Management School, Liverpool, UK

8Department of Public Health Pharmacy and Management, School of Pharmacy, Sefako Makgatho Health Sciences University, Ga-Rankuwa, Pretoria, South Africa

**Correspondence:**

Brian Godman

Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom.

Email: [Brian.godman@strath.ac.uk](mailto:Brian.godman@strath.ac.uk).

Telephone: +44-141-548-3825.

Fax: +44-141-552-2562

*Or*

Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden.

Email: [Brian.Godman@ki.se](mailto:Brian.Godman@ki.se).

Telephone: +46-8-58581068.

Fax: +46-8-59581070

**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.

**Keywords:** DOTS program, TB, predictors, Effectiveness, Outcomes

(Accepted for Publication Expert Review of Respiratory Therapy – please keep Confidential)

**1. Introduction**

Tuberculosis (TB) is the leading cause of death worldwide from an infectious disease1–3. 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 Namibia4. However, TB can be cured5–8, 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 20159,10. 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 Namibia11–15. Nevertheless, although TB incidence rates have been decreasing across countries, Namibia remains a high TB burdened country4. 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 decade11,15,17. TSR are even lower among the retreatment and smear negative cases13,18. 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 characteristics25–27.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 high9. 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 (χ2). 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 (%) | | χ2 | Cramer’s  V | p-value |
| **Successful** | **Unsuccessful** |
| Regions  Khomas  Erongo  Ohangwena  Oshikoto  Kavango West  Karas  Otjozondjupa  Omaheke  Zambezi  Hardap  Kunene  Kavango East  Oshana  Omusati | **N=76856**  15378(20.0)  9480 (12.3)  7520 (9.8)  7355 (9.6)  5595 (7.3)  4888 (6.4)  4638 (6.0)  3219 (4.2)  3057 (4.0)  3069 (4.0)  2456 (3.2)  1538 (2.0)  1858 (2.4)  6805 (8.9) | **61338(79.8)**  12105(78.7)  7588 (80.0)  5903 (78.5)  5885 (80.0)  4335 (77.5)  3859 (78.9)  3698 (79.7)  2822 (87.7)  2726 (89.2)  2522 (82.2)  1897 (77.2)  1135 (78.7)  1508 (81.2%)  5355 (78.7%) | **15518(20.2)**  3273(21.3)  1892 (20.0)  1617 (21.5)  1470 (20.0)  1260 (22.5)  1029 (21.1)  9402 (0.30)  397 (12.3)  331 (10.8)  547 (17.8)  559 (22.8)  403 (26.2)  350 18.8%  145021.3% | 393.3 | 0.07 | 0.000\* |
| MTP period  MTP-I  MTP-II | 36657  40199 | 28766(78.5)  32572(81.0) | 7891(21.5)  7627(19.0) | 77.6 | 0.03 | 0.000\* |
| DOT facility level  Hospital  Health Center  Clinic | 16189 (16.1)  12378 (16.1)  48289 (62.8) | 12348(76.3)  9750(78.8)  39240(81.3) | 3841(23.7)  2628(21.2)  9049(18.7) | 197.0 | 0.05 | 0.000\* |
| TB registration status  Previously registered  Patient not registered | 169 (0.23)  76687 (98.8) | 33(19.5)  61305(79.9) | 136(80.5)  15382(20.1) | 382 | 0.07 | 0.000\* |
| Gender  Female  Male | 32556(42.1)  44300(57.9) | 26352(80.9)  34986(79.0) | 6204(19.1)  9314(21.0) | 45.1 | 0.02 | 0.000\* |
| Patient’s age  0 - 04 years  05 – 14 years  15 – 24 years  25 - 34 years  35 - 44 years  45 – 54 years  55 – 64 years  65+ years | 4878(6.3)  4167(5.4)  9260(12.1)  21942(28.6)  18558(24)  9462(12.3)  4498(5.9)  4091(5.4) | 4191(85.9)  3729(89.5)  7766(83.9)  17564(80.0)  14467(78.5)  7292(77.1)  3355(74.6)  2874(70.3) | 687(14.1)  438(10.5)  1494(16.1)  4378(20.0)  3991(21.5)  2170(22.9)  1143(25.4)  1217(29.7) | 822.6 | 0.10 | 0.000\* |
| Patient aged < 5 years  Yes  No | 70415(91.6)  6441(8.4) | 5596(86.9)  55742(79.2) | 845(13.1)  14673(20.8) | 218.2 | 0.05 | 0.000\* |
| Treatment category  New patient  Retreatment | 62469(87.6)  9567(12.4) | 51161(81.9)  6695(70) | 11308(18.1)  2872(30.0) | 745.4 | 0.10 | 0.000\* |
| TB case registered  New patient  Failure  Previously treated  Readmission  Recurrent TB  Relapse TB | 62469(81.3)  675(0.9)  3508(4.6)  1043(1.4)  1313(1.7)  7848(10.2) | 51161(81.9)  370(54.8)  2509(71.5)  674(64.6)  974(74.2)  5650(72.0) | 11308(18.1)  305(45.2)  999(28.5)  369(35.4)  339(25.8)  2198(28) | 1053 | 0.11 | 0.000\* |
| Baseline sputum smear  Smear negative (-)  Smear positive (+)  Smear not done | 14453(18.8)  36358(47.3)  26042(33.9) | 11544(79.9)  29165(80.2)  20629(79.2) | 2909(20.1)  7193(19.8)  5416(20.8) | 9.7 | 0.01 | 0.008\* |
| Class of smear done  EPTB No smear  PTB No smear  PTB Smear negative (–)  PTB Smear negative (+) | 14733(19.2)  13457(17.5)  12325(16.0)  36341(47.3) | 11993(81.4)  10423(77.5)  9772(79.3)  29150(80.2) | 2740(18.6)  3034(22.5)  2553(20.7)  7191(19.8) | 75.3 | 0.03 | 0.000\* |
| Microscopy (Pre-treatment)  Negative -  Positive +  Missing result | 15971(20.8)  34839(45.3)  26046(33.9) | 12832(80.3)  27876(80.0)  20630(79.2) | 3139(19.7)  6963(20.0)  5416(20.8) | 9.6 | 0.01 | 0.008\* |
| TB Classification  EPTB  PTB | 14733(19.2)  62123(80.8) | 11993(81.4)  49345(79.4) | 2740(18.6)  12778(20.6) | 28.7 | 0.02 | 0.000\* |
| TB regimen initiated  2HRZE/4HR (A)  2HRZE/1HRZE/5HRE (A)  2HRZE/1HRZE/5HR (C)  2HRZ/4HR (C)  Other regimen | 57238(74.5)  14006(18.2)  342(0.45)  4914(6.4)  356(0.5) | 46673(81.5)  9883(70.6)  288(84.2)  4251(86.5)  243(68.3) | 10565(18.5)  4123(29.4)  54(15.8)  663(13.5)  113(31.7) | 1020 | 0.12 | 0.000\* |
| DOT supporter/type  Guardian (relat/neigh)  Workplace  Health Facility  Community H/Worker  Other | 28546(48.9)  682(1.2)  27410(46.9)  1409(2.4)  358(0.6) | 23480(82.3)  566(83.0)  21462(78.2)  1230(87.3)  257(71.8) | 5066(17.7)  116(17.0)  5948(21.7)  179(12.7)  101(28.2) | 201.6 | 0.06 | 0.000\* |
| HIV status  Negative  Positive  Unknown | 25476(44.0)  27704(47.9)  4676(8.1) | 21752(85.4)  21243(76.7)  3713(79.4) | 3724(14.6)  6461(23.3)  963(20.6) | 652.1 | 0.11 | 0.000\* |
| Patient on HAART  Yes  No | 16741(62.9)  9894(37.1) | 13184(78.8)  7713(78.0) | 3557(21.2)  2181(22) | 2.3 | 0.01 | 0.127 |
| HIV IPT exposure  Yes  No | 338(3.2)  10382(96.9) | 264(78.1)  8256(79.5) | 74(21.9)  2126(20.5) | 0.4 | 0.01 | 0.526 |
| HIV CPT exposure  No  Yes | 5065(17.6)  23773(82.4) | 4103(81.0)  18382(77.3) | 962(19.0)  5391(22.7) | 33 | 0.034 | 0.000\* |
| Developed MDR – TB  Yes  No | 565(0.6)  76291(99.4) | -  61338(80.4) | 565(100)  14953(19.6) | 2249.8 | 0.17 | 0.000\* |
| Sputum conversion- at 2months  To smear negative -  Defaulted  Died during treat  Remained positive +  Results not available  Patient transferred | 17835(49.2)  478(1.3)  1374(3.8)  2702(7.5)  13306(36.7)  556(1.5) | 16735(93.8)  -  -  1971(72.9)  10460(78.6)  - | 1100(6.2)  478(100)  1374(100)  731(27.1)  2846(21.4)  556(100) | 12068 | 0.58 | 0.000\* |
| Sputum conversion at 3months  To smear negative -  Defaulted  Died during treat  Remained positive +  Results not available  Patient transferred | 25262(69.7)  712(2.0)  1543(4.3)  2361(6.5)  5745(15.9)  628(1.7) | 23663(93.7)  -  -  1441(61%)  4062(70.7)  - | 155(6.3)  712(100)  1543(100)  920(39)  1683(29.3)  628(100) | 15587 | 0.66 | 0.000\* |
|  |  |  |  |  |  |  |

*\* = 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 (χ2 = 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 R2 score of 0.597 as well as a non-significant Hosmer and Lemeshow Test (χ2 = 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  MTP-II | 0.3 | 1 | 1.1(0.8,1.5)  1 | 0.608 |
| **Region**  Khomas  Kavango West  Zambezi  Otjozondjupa  Erongo  Karas  Hardap  Kunene  Ohangwena  Omaheke  Oshikoto  Oshana  Omusati  Kavango East | 36.0  2.1  1.0  2.0  6.3  1.0  0.5  0.7  2.5  2.4  0.8  0.0  0.4  1.4 | 13  1  1  1  1  1  1  1  1  1  1  1  1  1 | 2.8(0.7, 11.3)  0.8(0.4,1.3)  1.5(0.9,2.6)  2.8(1.3,6.4)  0.7(0.3,1.7)  0.7(0.3,1.7)  0.4(0.0,3.5)  0.6(0.3,1.1)  2.0(0.8,4.9)  0.7(0.3,1.6)  125109200  1.8(0.3,12.5)  1.4(0.8,2.6)  1 | 0.001\*  0.147  0.324  0.158  0.012\*  0.328  0.465  0.396  0.112  0.121  0.385  1.000  0.540  0.237 |
| **Facility level**  Hospital  PHC Clinic  Health Center | 1.7  1.1  1.6 | 2  1  1 | 1.4(0.8, 2.4)  1.3(0.9, 2.0)  1 | 0.428  0.287  0.211 |
| **Patients sex**  Male  Female | 1.7 | 1 | 0.8(0.6,1.1)  1 | 0.197 |
| **Patient age category**  0 to 04  05 to 14  15 to 24  25 to 34  35 to 44  45 to 54  55 to 64  65+ | 9.7  2.0  1.4  2.0  3.1  0.6  0.3  3.3 | 7  1  1  1  1  1  1  1 | 7.6(0.5,121.6)  2.4(0.6,10.5)  1.6(0.8,3.2)  1.7(0.9,3.2)  1.3(0.7,2.4)  1.2(0.6,2.3)  2.1(0.9,4.4) | 0.206  0.153  0.243  0.155  0.080  0.450  0.602  0.070 |
| **Previously registered**  No  Yes | 0.1 | 1 | 0.6(0.0,9.0)  1 | 0.726 |
| **Diagnostic classification**  Failure  Readmission  Relapse | 1.7  0.5  1.3 | 2  1  1 | 0.7(0.3,1.8)  0.6(0.3,1.4)  1 | 0.429  0.467  0.246 |
| Pulmonary  Lymph Nodes  Miliary  Other Sites  Pleura  Bones/Joints | 0.0  0.0  0.0  0.0  0.0  0.0 | 5  1  1  1  1  1 | 0.0(0.0,1.0)  1.3  0.4  0.4  0.0 | 1.000  0.999  1.000  1.000  1.000  0.999 |
| **DOT Provider**  Guardian (relative, neighbor)  Workplace  Health Facility  Community health worker  Other | 27.4  25.3  12.8  20.4  10.5 | 4  1  1  1  1 | 10.8(4.3,27.2)  25.6(4.3,151.8)  8.6(3.4,22.0)  10.6(2.5,44.4)  1 | 0.000\*  0.000\*  0.000\*  0.000\*  0.001\* |
| TB regimen initiated  2 HRZE/4 HR  2 HRZES/1 HRZE/5 HRE (Adults)  2 HRZ / 4 HR | 41.7  0.9  0.0  0.0 | 3  1  1  1 | 3.2(0.3,34.5)  1.0(0.1,11.1)  1 | 0.000\*  0.333  0.999 |
| Smear non conversion  Yes  No | 459.1 | 1 | 0.02(0.01,0.03)  1 | 0.000\* |
| Sputum conversion 2 months  Converted to smear negative  Remaining smear positive  Defaulted+Died+Transfered+Not available | 8.7  2.8  7.9 | 2  1  1 | 0.7(0.5,1.1)  0.5(0.3,0.8)  1 | 0.013\*  0.092  0.005 |
| **Antiretroviral Treatment**  No  Yes | 0.8 | 1 | 0.8(0.6,1.2)  1 | 0.363 |
| **Cotrimoxazole Prophylaxis**  No  Yes | 9.6 | 1 | 0.4(0.2,0.7)  1 | 0.002\* |
| **IPT (isoniazid) exposure**  No  Yes | 0.5 | 1 | 1.2(0.7,2.6)  1 | 0.464 |
| **HIV status**  Negative  Positive  Unknown | 26.1  0.1  12.1 | 2  1  1 | 1.1(0.5,2.2)  0.2(0.1,0.5)  1 | 0.000\*  0.813  0.001\* |
| 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 years17,29. 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 services31 are important drivers of poor TB treatment outcomes18,20,32. 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 strategy31.

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 Uganda25,26 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 used33. In addition, coinfection with HIV and/or diabetes among TB patients, patient related demographic characteristics34,35, and pharmacokinetic variability among populations36. 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 regimens37,38, HIV co-infection 39,40, adverse drug effects41–43 and the lack of screening and monitoring systems6,18,44,45.

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 age41,46 and male-gender27,46-49, 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 regimens36,41,50, 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 reactions43. 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.

**Funding**

This paper was not funded.

**Declaration of interest**

E. Ene is an employee of the Anoixis Corporation. In addition, R. Nunurai, F. Mavungha, A. Thomas, R. Amutenya and G. Gunther are employees of the Ministry of Health and Social Sciences in Namibia for the TB programme. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

**Reviewer disclosures**

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose**.**

***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.

# References

Papers of special note have been highlighted as:

\* of interest

\*\* of considerable interest

1. Republic of Namibia Ministry of Health and Social Services. National Guidelines for the Management of Tuberculosis, Third Edition. 2011. Available at URL: http://www.who.int/hiv/pub/guidelines/namibia\_tb.pdf

2. Corbett EL, Marston B, Churchyard GJ, De Cock KM. Tuberculosis in sub-Saharan Africa: Opportunities, challenges, and change in the era of antiretroviral treatment. Lancet. 2006;367(9514):926-937.

3. Lawn SD, Zumla AI. Tuberculosis. Lancet. 2011;378(9785):57-72

4. WHO. Use of high burden country lists for TB by WHO in the post-2015 era. 2015. Available at URL: http://www.who.int/tb/publications/global\_report/high\_tb\_burdencountrylists2016-2020summary.pdf

\*Key reference discussing the extent of TB across countries

5. WHO. The Stop TB Strategy: building on and enhancing DOTS to meet the TB-related Millennium Development Goals. 2006. Available at URL: http://apps.who.int/iris/bitstream/handle/10665/69241/WHO\_HTM\_STB\_2006.368\_eng.pdf?sequence=1&isAllowed=y

6. Thiam S, LeFevre AM, Hane F, Ndiaye A, Ba F, Fielding KL, et al. Effectiveness of a strategy to improve adherence to tuberculosis treatment in a resource-poor setting: a cluster randomized controlled trial. Jama. 2007;297(4):380-6

7. World Health Organization. What Is DOTS ? A Guide to Understanding the WHO-Recommended TB Control Strategy Known as DOTS. 1999. Available at URL: http://apps.who.int/iris/bitstream/handle/10665/65979/WHO\_CDS\_CPC\_TB\_99.270.pdf?sequence=1&isAllowed=y

8. Borgdorff MW, Floyd K, Broekmans JF. Interventions to reduce tuberculosis mortality and transmission in low- and middle-income countries. Bull World Health Organ. 2002;80(3):217-227.

9. WHO. GLOBAL TUBERCULOSIS REPORT. 2016. Available at URL: http://apps.who.int/medicinedocs/documents/s23098en/s23098en.pdf

\*Key WHO update discussing the extent of TB across countries

10. Tanday S. Will we ever eliminate tuberculosis, the voiceless disease? Lancet Respir Med. 2017. Mar 15

11. van Gorkom J, Mavhunga F, Omer OA, et al. TB control in Namibia 2002-2011: Progress and technical assistance. Open Infect Dis J. 2013;7(SPEC ISS1):23-29

\*Good paper outlining progress in TB control in Namibia in recent years

12. Baltussen R, Floyd K, Dye C. Cost effectiveness analysis of strategies for tuberculosis control in developing countries. BMJ. 2005;331(7529):1364

13. Republic of Namibia Ministry of Health and Social Services. Republic of Namibia Ministry of Health and Social Services National Tuberculosis and Leprosy Programme Annual Report : 2014-2015. Windhoek; 2015.

\*Good update documenting approaches in Namibia to help treat TB

14. Laxminarayan R, Klein EY, Darley S, Adeyi O. Global investments in TB control: Economic benefits. Health Aff. 2009;28(4):w730-42

15. Ministry of Health and Social Services. National Tuberculosis and Leprosy Programme Summary Report 2014-15. 2015.

16. WHO. WHO | Tuberculosis. WHO. 2016. Avaulable at URL: http://www.who.int/mediacentre/factsheets/fs104/en/.

17. World Health Organization. Global Tuberculosis Report 2016.

18. Studies H, Ehlers U, Unisa HS. Factors associated with community-based TB care in the omaheke region, Namibia. 9(1):59-72.

19. WHO. MDR-TB. Available at URL: http://www.who.int/tb/challenges/mdr/MDR-RR\_TB\_factsheet\_2017.pdf.

20. Zvavamwe Z, Ehlers VJ. Experiences of a community-based tuberculosis treatment programme in Namibia: A comparative cohort study. Int J Nurs Stud. 2009;46(3):302-309

21. Seeling S, Mavhunga F, Thomas A, Adelberger B, Ulrichs T. Barriers to access to antiretroviral treatment for HIV-positive tuberculosis patients in Windhoek, Namibia. Int J Mycobacteriology. 2014;3(4):268-275.

22. DeRiemer K, García-García L, Bobadilla-del-Valle M, et al. Does DOTS work in populations with drug-resistant tuberculosis? Lancet. 2005;365(9466):1239-1245.

23. Huynh GH, Klein DJ, Chin DP, et al. Tuberculosis control strategies to reach the 2035 global targets in China: the role of changing demographics and reactivation disease. BMC Med. 2015;13(1):88.

24. Acosta CD, Rusovich V, Harries AD, Ahmedov S, van den Boom M, Dara M. A new roadmap for childhood tuberculosis. Lancet Glob Heal. 2014;2(1):e15-7

25. Nakiyingi L, Bwanika JM, Kirenga B, et al. Clinical Predictors and Accuracy of Empiric Tuberculosis Treatment among Sputum Smear-Negative HIV-Infected Adult TB Suspects in Uganda. PLoS One. 2013;8(9).

26. Namukwaya E, Nakwagala FN, Mulekya F, Mayanja-Kizza H, Mugerwa R. Predictors of treatment failure among pulmonary tuberculosis patients in mulago hospital, Uganda. Afr Health Sci. 2011;11 Suppl 1:S105-11

27. Waitt CJ, Squire SB, C.J. W, S.B. S. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis. 2011;15(7):871-885.

28. WHO. Best Practices in Prevention, Control and Care for Drug Resistant Tuberculosis. 2017.Available at URL: http://www.euro.who.int/\_\_data/assets/pdf\_file/0020/216650/Best-practices-in-prevention,control-and-care-for-drugresistant-tuberculosis-Eng.pdf

29. MoHSS. Republic of Namibia Ministry of Health and Social Services National Tuberculosis and Leprosy Programme Annual Report : 2014-2015. 2015.

30. Kapoor SK, Raman AV, Sachdeva KS, Satyanarayana S. How did the TB patients reach DOTS services in Delhi? a study of patient treatment seeking behavior. PLoS One. 2012;7(8)

31. Uplekar M, Weil D, Lonnroth K, et al. WHO’s new end TB strategy. Lancet. 2015;385(9979):1799-1801.

\*\* Good paper outlining potential strategies to eradicate TB

32. MUJASI PN, Matlakala MC Factors Associated With Health Seeking Behaviour of Pulmonary Tuberculosis Patients in Butaleja District in Uganda. African Journal for Physical Health Education, Recreation and Dance. 2014;20(3):841-57

33. Oxlade O, Piatek A, Vincent C, Menzies D. Modeling the impact of tuberculosis interventions on epidemiologic outcomes and health system costs. BMC Public Health. 2015;15(1):141.

34. Sesay ML. Patient Characteristics and Treatment Outcomes Among Tuberculosis Patients in Sierra Leone. 2017. Available at URL: https://scholarworks.waldenu.edu/cgi/viewcontent.cgi?article=4680&context=dissertations

35. Chida N, Ansari Z, Hussain H, et al. Determinants of default from tuberculosis treatment among patients with drug-susceptible tuberculosis in Karachi, Pakistan: A mixed methods: Study. PLoS One. 2015;10(11):1-14.

36. 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. Eur J Clin Pharmacol. 2016;72(8):905-916.

37. Marx FM, Dunbar R, Enarson DA, Beyers N. The Rate of Sputum Smear-Positive Tuberculosis after Treatment Default in a High-Burden Setting: A Retrospective Cohort Study. PLoS One. 2012;7(9):1-9.

38. Lienhardt C, Manneh K, Bouchier V, Lahai G, Milligan PJM, McAdam KPWJ. Factors determining the outcome of treatment of adult smear-positive tuberculosis cases in The Gambia. Int J Tuberc Lung Dis. 1998;2(9):712-718.

39. Sinshaw Y, Alemu S, Fekadu A, Gizachew M. Successful TB Treatment Outcome and Its Associated Factors among TB/HIV Co-Infected Patients Attending Gondar University Referral Hospital, Northwest Ethiopia: An Institution Based Cross-Sectional Study. Vol 17. [BMC Infect Dis.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Successful+TB+Treatment+Outcome+and+Its+Associated+Factors+among+TB%2FHIV+Co-Infected+Patients+Attending+Gondar+University+Referral+Hospital%2C+Northwest+Ethiopia) 2017;17(1):132

40. van Hest R, Ködmön C, Verver S, et al. Tuberculosis treatment outcome monitoring in European Union countries: systematic review. Eur Respir J. 2013;41(3):635-643.

41. Choi R, Jeong B-H, Koh W-J, Lee S-Y. Recommendations for Optimizing Tuberculosis Treatment: Therapeutic Drug Monitoring, Pharmacogenetics, and Nutritional Status Considerations. Ann Lab Med. 2017;37(2):97. d

\*Good paper to help improve care of patients with TB

42. Baboli MT, Abdolmaleki EY, Shirzad M, Samakoosh MA, Ghasemian R. Prevalence of drug-induced hepatitis and its risk factors in the treatment of tuberculosis in TB infected patients attending Razi hospital, 2006-2011. [Persian]. J Maz Univ Med Sci. 2014;24(109):235-240.

43. Sagwa E, Mantel-Teeuwisse AK, Ruswa N, et al. The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia. South Med Rev. 2012;5(1):6-13.

\*\*Interesting paper outlining the nature and extent of ADRs furing treatment of patients with drug-resistant TB in Namibia

44. Garfein RS, Collins K, Muñoz F, et al. Feasibility of tuberculosis treatment monitoring by video directly observed therapy: A binational pilot study. Int J Tuberc Lung Dis. 2015;19(9)

45. Espinal MA, Kim SJ, Suarez PG, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. Jama. 2000;283(19):2537-2545

46. Vasankari T, Holmstrom P, Ollgren J, Liippo K, Kokki M, Ruutu P. Risk factors for poor tuberculosis treatment outcome in Finland: a cohort study. [BMC Public Health.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Risk+factors+for+poor+tuberculosis+treatment+outcome+in+Finland%3A+a+cohort+study) 2007 Oct 14;7:291.

47. Hung CL, Chien JY, Ou CY. Associated factors for tuberculosis recurrence in Taiwan: A nationwide nested case-control study from 1998 to 2010. PLoS One. 2015;10(5):1-11

48. Gomes NM de F, Bastos MC da M, Marins RM, et al. Differences between Risk Factors Associated with Tuberculosis Treatment Abandonment and Mortality. Pulm Med. 2015;2015:1-8

49. Oshi DC, Oshi SN, Alobu I, Ukwaja KN. Profile, Outcomes, and Determinants of Unsuccessful Tuberculosis Treatment Outcomes among HIV-Infected Tuberculosis Patients in a Nigerian State. Tuberc Res Treat. 2014;2014:202983

50. Sotgiu G, Alffenaar J-WC, Centis R, et al. Therapeutic drug monitoring: how to improve drug dosage and patient safety in tuberculosis treatment. Int J Infect Dis. 2015;32:101-104

**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*