EFFECTIVENESS OF THE COMMUNITY-BASED DOTS STRATEGY ON TUBERCULOSIS TREATMENT SUCCESS RATES IN NAMIBIA

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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.

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.

METHODS

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 base on TB guidelines, which are implemented at all DOT sites with supported training. These annual rates are based on aggregates of quarterly reports collated 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.

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 in **Supplement A**. 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 in **Supplement B**.

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 and the University of Namibia.

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.

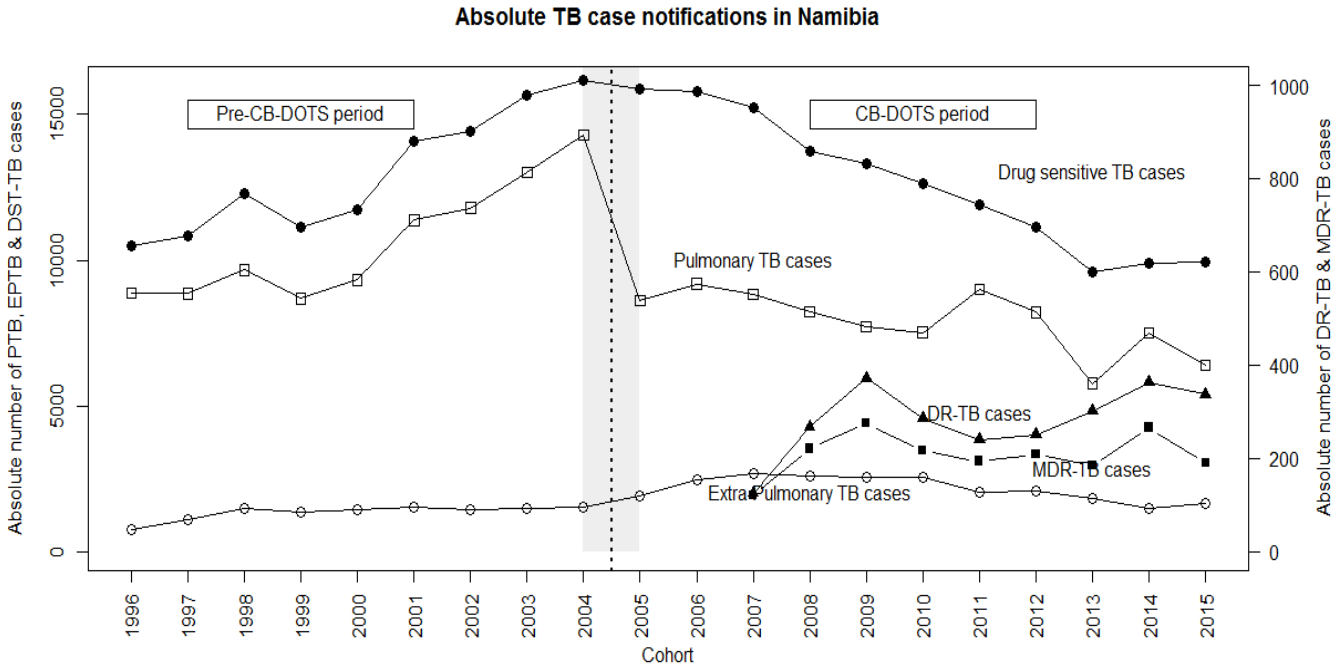

Figure 1: Annual number of cases of drug susceptible tuberculosis (DST-TB, ●), drug resistant tuberculosis (MDR-TB, ▲), multi-drug resistant tuberculosis (MDR-TB, ■), pulmonary tuberculosis (PTB, □) and extrapulmonary tuberculosis (EPTB, ○), during the period 1996-2015.

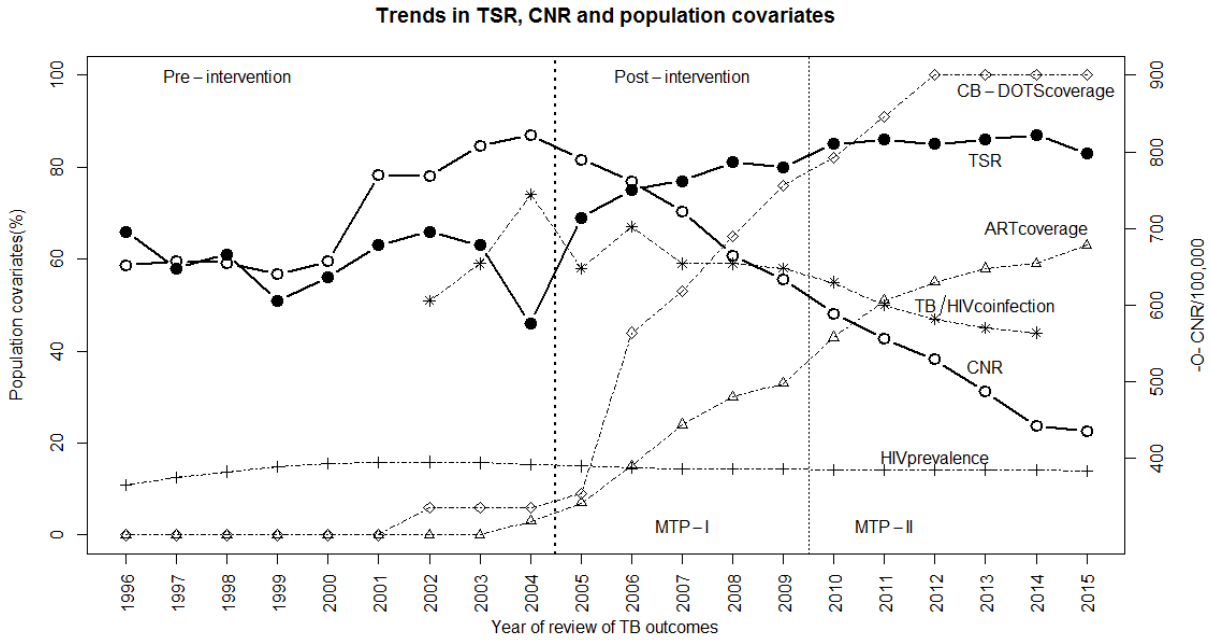

Figure 2: Annual case notification rates (CNR,O), CB-DOTS coverage (◇), adult HIV prevalence (+), ART coverage (△) and prevalence of HIV among TB patients (∗), and treatment success rate (TSR, ●) during the period 1996-2015. Data source: Annual MoHSS National TB and Leprosy reports, Global TB reports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

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.

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).

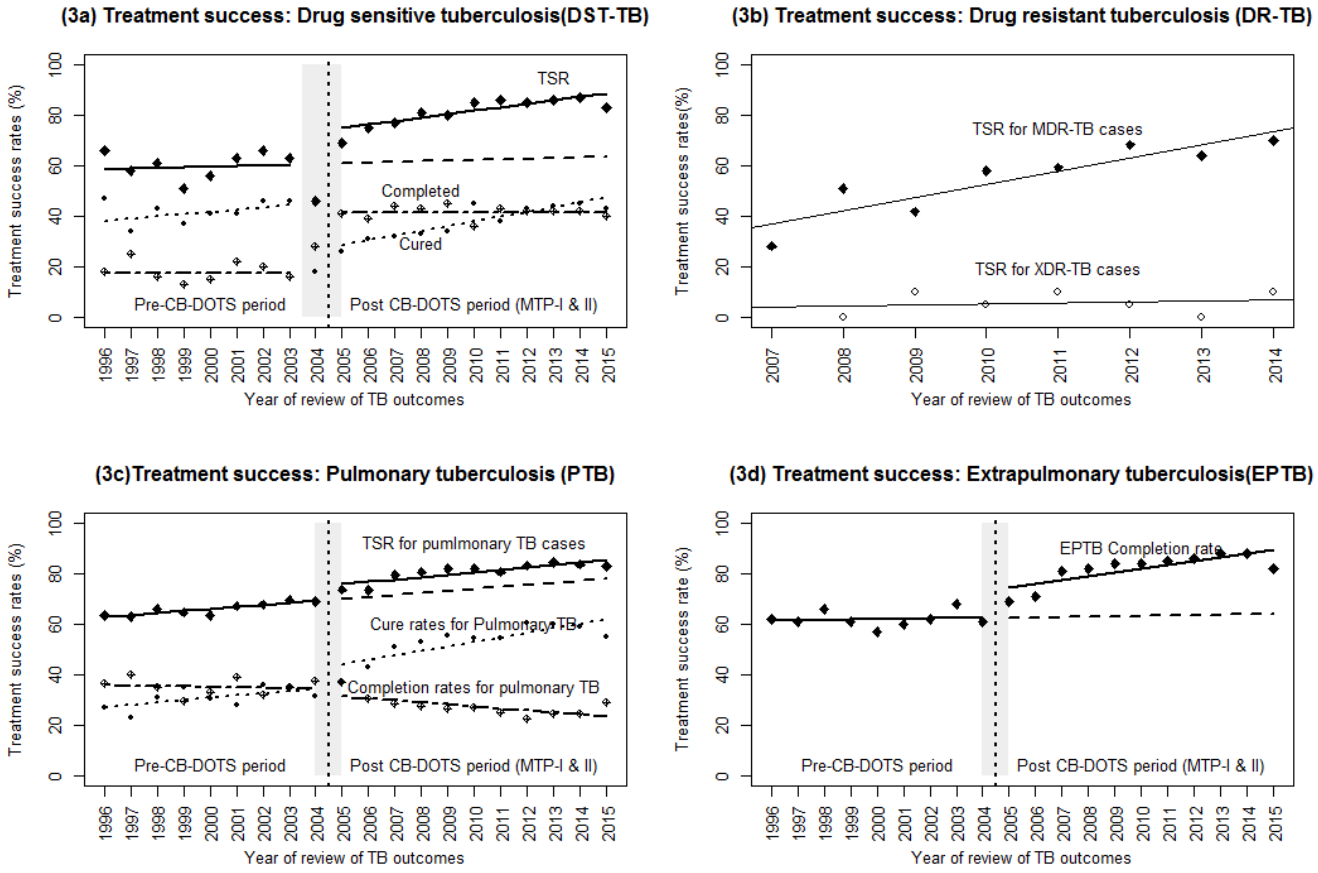

Figure 3: Interrupted time series analysis of the annual treatment success rate (■), cure rate (●), and treatment completion rate (◈).The predicted pre- and post-intervention trends, based on the final segmented regression model, are shown by the lines.

Table 1: 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 Treatm ent completion 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 st atistic 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.*

After the intervention there was a significant (p<0.005) immediate increase in level and/or annual rates for treatment outcomes for pulmonary versus extrapulmonary (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).

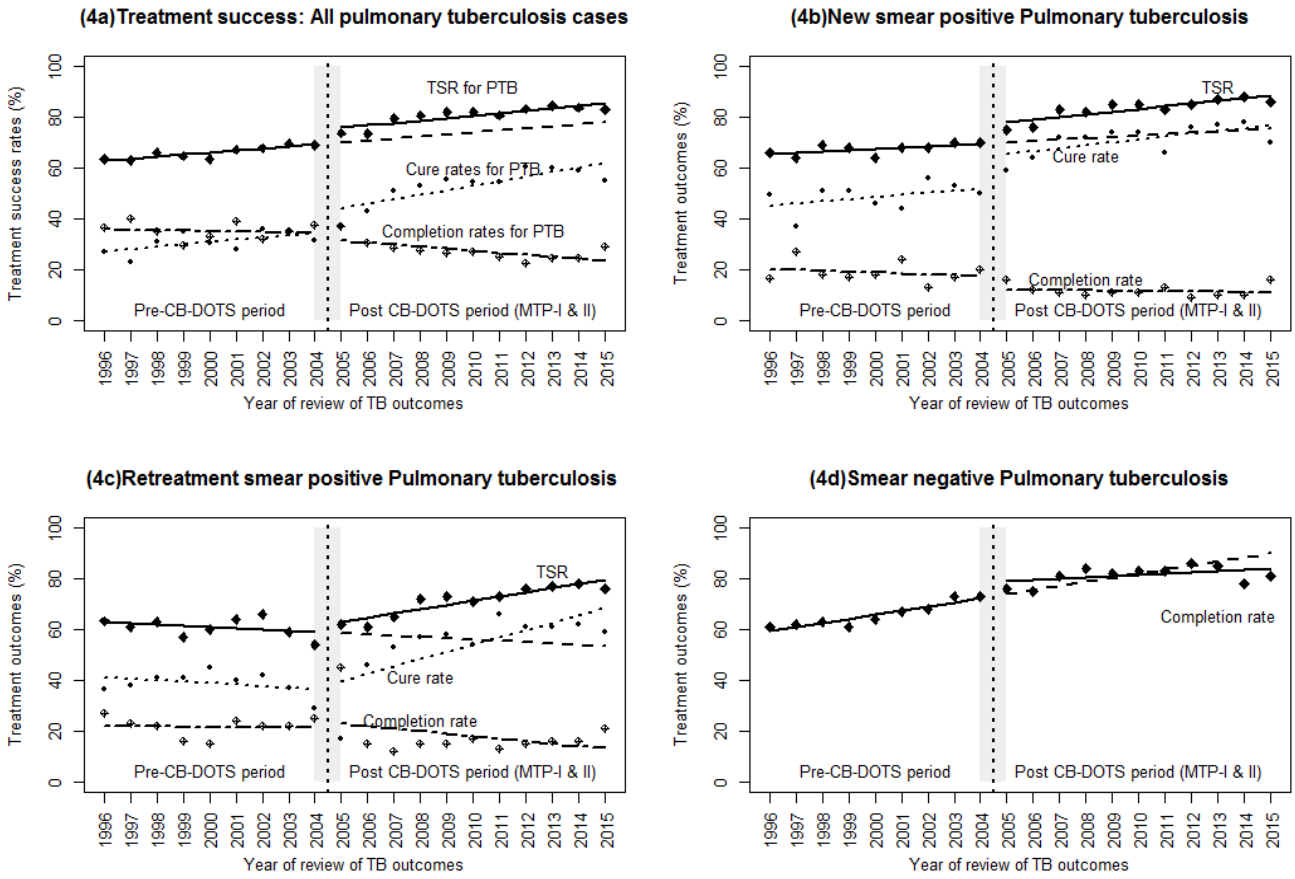

Figure 4: Interrupted time series analysis of the annual treatment success rates (◆), cure rates (●), and treatment completion rates (◇) by PTB categories, i.e. new smear positive cases, retreatment cases and negative smear patients. The predicted pre- and post-intervention

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.

Table 2: Impact of population time varying co-variates on treatment success, cure, treatment completion and case notification 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 (DST-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.

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) current interventions (**Supplement C,** 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.

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 approaches to optimise treatment outcomes.

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.

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Supplement A

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 cured and 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_2) 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.

Supplement B

Facility-based and community-based DOTS in Namibia

Namibia achieved a country-wide 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 (upto 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 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 such as

family/relatives or workplace peers or CHW directly observe the administration of the TB-medication at community DOT points, households and workplaces. For instance, in 2015 in the Omaheke region there were, 954 DOT supporters, 858 supervisors and 1189 DOT providers 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 quality assured bacteriology laboratories from 30 (1 lab per 67,000 people) in 2004 to 36 out 80 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.

Supplement C

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.

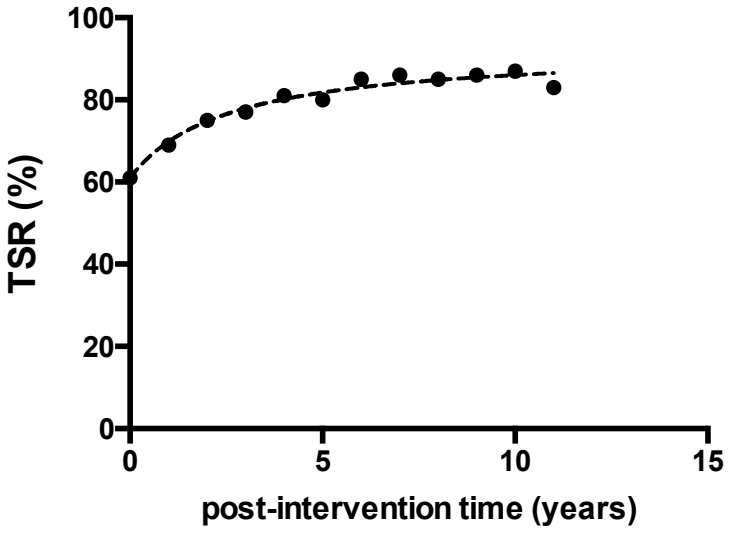

Figure 5: The maximum effect model fitted the post-intervention treatment success rates (TSR) very well (r^2 = 0.961) with a predicted maximum TSR of 92.4%.