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Comparing early treatment outcomes of MDR-TB in a decentralised setting with a centralised setting in KwaZulu-Natal, South Africa

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Abstract

Setting—In KwaZulu-Natal, South Africa, a TB and HIV endemic setting, prolonged hospitalisation for the treatment of the growing number of MDR-TB patients is not possible or effective.

Objective—We compared early treatment outcomes in patients with MDR-TB, with and without HIV co infection, at a central, urban, referral hospital with four decentralised rural sites.

Design—This is an operational, prospective cohort study of patients between 1 July 2008 to 30 November 2009, where culture conversion, time-to-culture-conversion, survival and predictors of these outcomes were analysed.

Results—Of the 860 patients with MDR-TB, 419 were at the decentralised sites and 441 at the central hospital. Overall, 71% were HIV co-infected.

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Contributors
Conceived and designed the study: ML, KW, AV, BM, IM, JB, NP.
Performed the study: ML, KW, BM, IM, JB
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Wrote the paper: ML, KW, AV, JB, KC, NP

Conflicts of interest
We declare that we have no conflicts of interest.

In the 17 month study period, there was a higher proportion of culture conversion at the decentralised sites compared with the centralised hospital (54% vs. 24%; P<0.001; Odds Ratio 3.76, 95% CI 2.81 – 5.03).

The median time to treatment initiation was significantly shorter at the decentralised sites compared with the centralised hospital (72 vs 93 days; p<0.001). There was no significant difference in survival following treatment initiation.

Conclusion—This study shows that early treatment outcomes suggest that decentralised care for MDR-TB patients is superior to that in a centralised setting.

Keywords

operational research; high burden of TB and HIV

BACKGROUND

The province of KwaZulu-Natal has South Africa's highest recorded tuberculosis (TB) incidence, 1163 per 100 000 population, in a setting where 80% of all TB patients are HIV positive and the HIV prevalence is amongst the highest in the world at 17%.[1, 2] The high prevalence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) in this setting is partly due to a poorly functioning TB control programme and ongoing nosocomial transmission.[3–5] MDR-TB is defined as TB resistant to at least isoniazid and rifampicin and XDR-TB is defined as MDR-TB with additional resistance to any fluorquinolone and at least one injectable second-line TB drug (amikacin, kanamycin or capreomycin).[6] In KwaZulu-Natal, drug susceptibility testing (DST) of positive cultures is performed routinely for isoniazid, rifampicin, ethambutol, streptomycin, kanamycin and ciprofloxacin.

Until 2008 the treatment of drug-resistant TB in KwaZulu-Natal mirrored the World Health Organization (WHO) guidelines patients underwent prolonged hospitalisation in a centralised, specialist TB hospital, followed by monthly outpatient visits to the same institution.[6] However, the overwhelming and escalating burden resulted in inconsistent guideline implementation. With limited beds at the centralised hospital, treatment initiation was often delayed by two to three months. When admitted, MDR- and XDR-TB patients were in mixed congregate wards from four to six months because of space limitations. Once discharged, the centralised hospital lacked the necessary personnel and infrastructure to address adverse effects and socio-economic demands of patients travelling from across the province.[7] Consequently, of the 5165 MDR-TB patients treated between 1994 and 2004, 67% had unsuccessful treatment outcomes, of which 14% defaulted and 19% were not evaluated.[8]

The KwaZulu-Natal Department of Health, identifying the need for alternative MDR-TB treatment models, began piloting decentralised care in 2008 at four sites across the province, utilizing regional district hospitals for initial hospitalisation and monthly outpatient follow-up.[9, 10] Furthermore, unlike the centralised model, district healthcare workers and community resources were recruited to strengthen outpatient follow-up. Although similar models of decentralised MDR-TB treatment have been successfully implemented in other countries,[11, 12] KwaZulu-Natal is uniquely challenged as the epicentre of both the TB and HIV epidemics insub-Saharan Africa.[5]

To determine the impact of decentralised MDR-TB treatment, we compare early treatment outcomes in the decentralised care model with the centralised treatment programme.

METHODS

Setting

South Africa has a district health system in which community-based clinics provide primary level care, and refer patients to district and regional hospitals for secondary level care. One aim of decentralised MDR-TB care was to create accessible treatment sites close to the patient's home. The four rural decentralised MDR TB sites are geographically positioned throughout the Province with a strategic focus on areas with the highest incidence of MDR-TB(Figure I).[13] The populations of these four sites are amongst the most socio-economically challenged in the country with limited or no access to piped water.[14]

Situated in the biggest urban centre of the Province, the centralised specialist TB hospital functions as the referral hospital for drug-resistant TB in KwaZulu-Natal. Currently the inpatient population consists almost exclusively of patients with drug-resistant TB.

By mid-2008 staff were deployed in the decentralised sites and area doctors trained to initiate and manage MDR-TB. More complicated patients such as children and patients with XDR-TB, are referred to the centralised hospital for treatment initiation and continued care. Guidelines on decentralised care were developed by the health department and circulated to the four decentralised sites before treatment commenced.[9] In accordance with South African national treatment guidelines, all patients receive a standardized MDR-TB regimen (pyrazinamide, ethambutol, ethionamide, kanamycin, ofloxacin and cycloserine).

Study Design

An operational prospective cohort study was implemented in 2009. Patients were included in the study if they were older than 18 years and had a laboratory confirmed diagnosis of MDR-TB.[15] Patients with XDR-TB, mono- or poly-resistant TB, and those receiving care at both a decentralized site and the centralized hospital were excluded. Inclusion criteria at the decentralised sites required that patients come from within the catchment area of the site. For the centralised hospital, patients were excluded if they were involved in clinical trials (Figure II). Patients who commenced treatment between 1 July 2008 and 30 November 2009 were included in the study. Patient follow-up ended when a treatment outcome was recorded, or 30 November 2009 when data was extracted for the interim analysis, whichever occurred first.

The primary outcome was the proportion of MDR-TB patients who culture converted in the decentralised sites compared to the centralised shospital. Conversion of sputum culture from positive to negative is considered a useful early indicator of programme effectiveness, as treatment outcomes are only available 18–24 months after treatment starts.[16, 17] Culture conversion is defined as two consecutive negative sputum cultures taken at least one month apart.[18] Secondary outcomes include time-to-conversion, treatment-initiation-delay, and survival. Time-to-culture-conversion is the time interval between the treatment start date and the date for the first of two consecutive negative sputum cultures. Treatment-initiation-delay is the time interval between the initial sputum collection for culture and treatment start date. This definition is an adaptation of the WHO definition as diagnostic date was not routinely recorded in KwaZulu-Natal. Treatment outcomes are based on standard WHO definitions.[18, 19] Patients were considered to have failed treatment if two or more drugs were replaced in the MDR-TB regimen, treatment was terminated due to adverse events, or there was no clinical improvement with either no culture conversion or reversion after initial conversion.[20]

Data collection and analysis

Clinical and laboratory data were continually recorded at all sites by assigned data capturers, including: demographic characteristics; previous exposure to TB treatment; HIV status and antiretroviral (ART) regimen; DST results; MDR-TB treatment regimens, treatment outcomes and monthly sputum culture results. Data was collected in MS Excel 2004 (Microsoft Corp) and analysis performed using STATA/SE version 11.0.

The comparison of the odds of culture conversion between sites, was assessed through computation of the odds ratio. The effect of all variables listed in Tables I and II were analysed using logistic regression models. Categorical data were analysed using Fisher's exact or Chi square test. Unpaired t-tests, the Wilcoxon two-sample test and Kruskal-Wallis nonparametric test were used for the analysis of continuous data. The Kaplan-Meier product limit method was used to calculate probabilities of culture conversion at different time points, and the log-rank test used to compare these probabilities by site. The duration of follow up was calculated as the number of days from treatment initiation to treatment outcome or 30 November 2009, whichever occurred first. Cox proportional hazards regression models were fitted to determine risk factors associated with outcomes in time-to-event-based analyses. The proportionality assumption of the Cox models was tested with ln(ln [survival]) curves and regression of scaled Schoenfeld residuals on functions of time. Variables not satisfying the proportional hazards assumptions were included as strata in the stratified Cox proportional hazards model.

This study protocol was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (Ref:BF052/09).

RESULTS

Between 1 July 2008 and 30 November 2009, 1647 patients started treatment for drug-resistant TB in KwaZulu-Natal. Eight hundred and sixty (860)MDR-TB patients met eligibility criteria - 419 at the decentralised sites and 441 at the centralised hospital (Figure II). Table I presents baseline characteristics of participants. The decentralised and centralised cohorts were comparable in terms of gender, age and HIV status. Co-infection was high at the decentralised sites and centralised hospital (79% vs 75%; P=0.306). A significantly higher number of patients at the decentralised sites were on ART or commenced ART within two weeks of MDR-TB treatment initiation (P<0.001). The decentralised site also had a higher proportion of smear positive patients at the time of MDR-TB diagnosis (P<0.001), a lower proportion had previous TB treatment (P<0.001)and a lower proportion were on a MDR-TB regimen of sixor more drugs (P<0.001) (Table II). The median duration of follow-up was 154 days (IQR:48–296).

Culture conversion at the decentralised site occurred more often (54% vs. 24%; P<0.001) and decentralised patients were more likely to culture convert in comparison to the centralised hospital patients (Odds Ratio (OR): 3.76, 95% CI 2.81–5.03). Not having a previous TB episode was the only significant predictor of culture conversion (OR 2.47, 95% CI 1.63–3.73). Fewer patients at the decentralised sites had a history of TB compared with the centralised hospital patients (60% vs. 96%; P<0.001).

Utilizing Kaplan-Meier curves there was no difference in the probability of culture converting over time between the decentralised sites and the centralised hospital (P=0.171) (Figure III). The methodology governing the computation of Kaplan-Meier probability estimates differs from the method used to generate culture conversion. Site, classified as either decentralised or centralised, did not satisfy the proportional hazards assumption, and hence a stratified Cox model was used to assess predictors of time-to-culture conversion

while controlling for site. Although HIV status was not identified as a predictor of time-to-culture-conversion, separate analyses were conducted for HIV-negative and HIV-positive patients as HIV status significantly impacts MDR-TB treatment outcomes.[21] In univariate analyses of HIV-negative individuals, being female (HR females vs males: 1.62, 95% CI 1.01–2.60) and increased weight (HR 1.03, 95% CI 1.01–1.06) were associated with a shorter time-to-culture conversion.

The median treatment-initiation-delay was significantly shorter at the decentralised sites compared to the centralised hospital (72 vs 93 days, P<0.001) (Table II).

Overall, 16% (67/419) of patients in the decentralised sites died, significantly more than the 7% (30/441) of patients in the centralised hospital (P<0.001) (Table III). Decentralised patients initiated therapy significantly earlier (72 days vs 93 days, P<0.001). The only significant predictor of death was age (HR 1.04, 95% CI 1.02–1.06).

The median time-to-death at the decentralised sites was 85 days (IQR 21–186) compared with 43 days (IQR: 11–100) at the centralised hospital. In time-to-event analysis, there was no significant difference in the probability of survival between the decentralised sites and the centralised hospital (Figure IV, P=0.095). In the univariate analysis, site was not significantly associated with time-to-death (HR 1.00, 95% CI 0.62–1.62).

DISCUSSION

This study suggests that decentralised care for MDR-TB patients is more effective than care in a centralised hospital. Significantly more patients culture converted at the decentralised sites (54%) than at the centralised hospital (24%) (P<0.001) (OR: 3.76, 95% CI 2.81–5.03). However, the probability of survival did not differ between the two models of care (P=0.095).

Successful treatment of MDR-TB patients in a decentralised setting was first documented in Peru.[12,22] More recently, three studies from southern Africa have confirmed that culture conversion is possible in HIV co-infected patients in a decentralised setting.[23–25] However, the cohorts in these studies were small and lacked a comparison group. In Lesotho, culture conversion was documented in 68% of 77 study patients.[23] In two rural South African settings, culture conversion was documented in 88% of the 45 patients in Tugela Ferry[24] and in 83% of the 53 patients in Hlabisa.[25] Our initial analysis of culture conversion suggests that decentralised care is more effective than centralised care in treating MDR-TB patients. Possible reasons as to why our culture conversion was lower than in the three other southern African studies referred to are that our study sample was far larger and implemented within the routine health services with minimal use of external resources.

Concurrent ART and TB treatment has been shown to improve treatment outcomes in patients co-infected with drug-resistant TB and HIV.[26, 27] Possible reasons for the lower culture conversion at the centralised hospital include longer treatment-initiation-delay, more patients with a history of TB and fewer patients on ART. In addition the decentralised sites have initiated vigorous outpatient programmes utilising mobile injection teams and local clinics to administer drugs in the injectable phase of treatment, educating the patient and their family about MDR-TB and HIV and introducing follow-up procedures for patients missing monthly appointments. At the centralised hospital patients are often discharged before the completion of the injectable phase and lack the intensive educational curriculum as the large volume of patients and geographical dispersion prohibits and effective outpatient programme. The uncertain and irregular provision of the daily injectable may contribute to the lower culture conversion at the centralised hospital.

To curb the MDR-TB epidemic early commencement of appropriate treatment is essential in limiting transmission of drug-resistant forms of *Mycobacterium tuberculosis*. DST results should be available between 42 and 56 days.[28] However, the median treatment-initiation-delay was 72 days and 93 days at the decentralised sites and the centralised hospital respectively (P<0.001). The shorter treatment-initiation-delays at the decentralised sites suggest that if treatment is accessible to patient's homes, treatment delays can be minimised (Table II). This is an improvement to the mean treatment-initiation-delay of 111 days documented in a 2007 study,[13] but further reductions are needed, as mortality rates of 40% within 30 days of sputum collection in MDR-TB patients have been documented in the province.[29]

Only unsuccessful treatment outcomes were available for the interim analysis as patients who were responding to treatment were still on treatment at the time data was extracted for analysis. More patients treated at decentralised sites died, compared to the centralised hospital. We expected better survival at the decentralised sites given that delays in treatment-initiation were shorter and the probability of culture conversion higher. One possible explanation is that twice the proportion of patients at the centralised hospital were lost to follow up (Table III), and the number of deaths at the centralised hospital probably unrecorded. (Patients at the centralised hospital for whom there was no data in the six months prior to data extraction were classified as lost to follow up and not as defaulters due to delays in data capturing). In contrast close follow up and contact with patients and their family at the decentralised sites made it possible to record "death" and "default".

There was a lack of association between death and HIV-status. This may be true as many of the HIV-infected patients were on ART (36/67 (54%)). However, this may not be true as there was missing data on HIV status in 13 (14%) of those who died. To achieve optimal MDR-TB outcomes ongoing barriers such as long delays in diagnosis, limited integration with HIV services and poor adherence to medication need to be addressed.

The current study is pragmatic in that the intervention being implemented utilises pre-existing management and clinical staff resources, and subsequent evaluation was conducted with minimal use of external resources. This is the ideal context in which to evaluate effectiveness, as it reflects the reality of implementation in resource-constrained settings and can inform roll out of the programme in public health settings.[30, 31] The rigorous monitoring process of this evaluation has ensured that challenges and successes have been brought to the attention of the provincial TB managers in a timely fashion and that the successes atone site are shared with the other sites.

However, an operational study presents both methodological and practical challenges, as the researcher had limited control over the design, scope and quality of the intervention. A further weakness of the study is that data routinely collected by health workers is at times incomplete and inaccurate. In some instances baseline (start of treatment) culture results were not available. In these instances diagnostic culture results were used as the baseline results and time-to-conversion calculated from the date treatment started. Some patients may have converted earlier. In addition, delays in data capturing at the centralised hospital may have resulted in fewer deaths being recorded. This paper is limited as it reports early outcomes, which may be misleading.

CONCLUSION

To our knowledge, this is the largest cohort reported worldwide, of MDR-TB patients in an HIV endemic area treated in a decentralised setting. Early results from this operational study suggest that decentralised care is feasible and initially superior to centralised care in treating

MDR-TB patients in an area with a high HIV-prevalence. However, final treatment outcomes at the end of two years of treatment will be necessary to definitively demonstrate the effectiveness of decentralised care.

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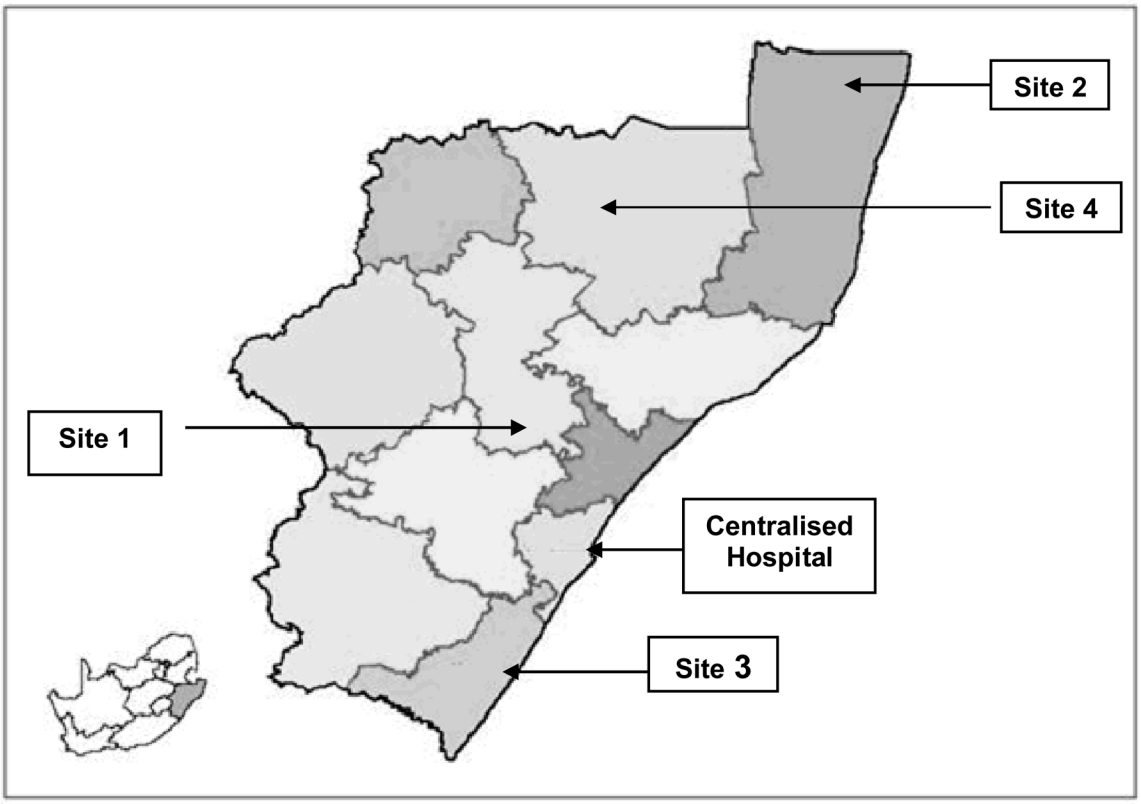


Figure I.
A map of KwaZulu-Natal showing the location of the centralised hospital and the four decentralised MDR-TB treatment sites

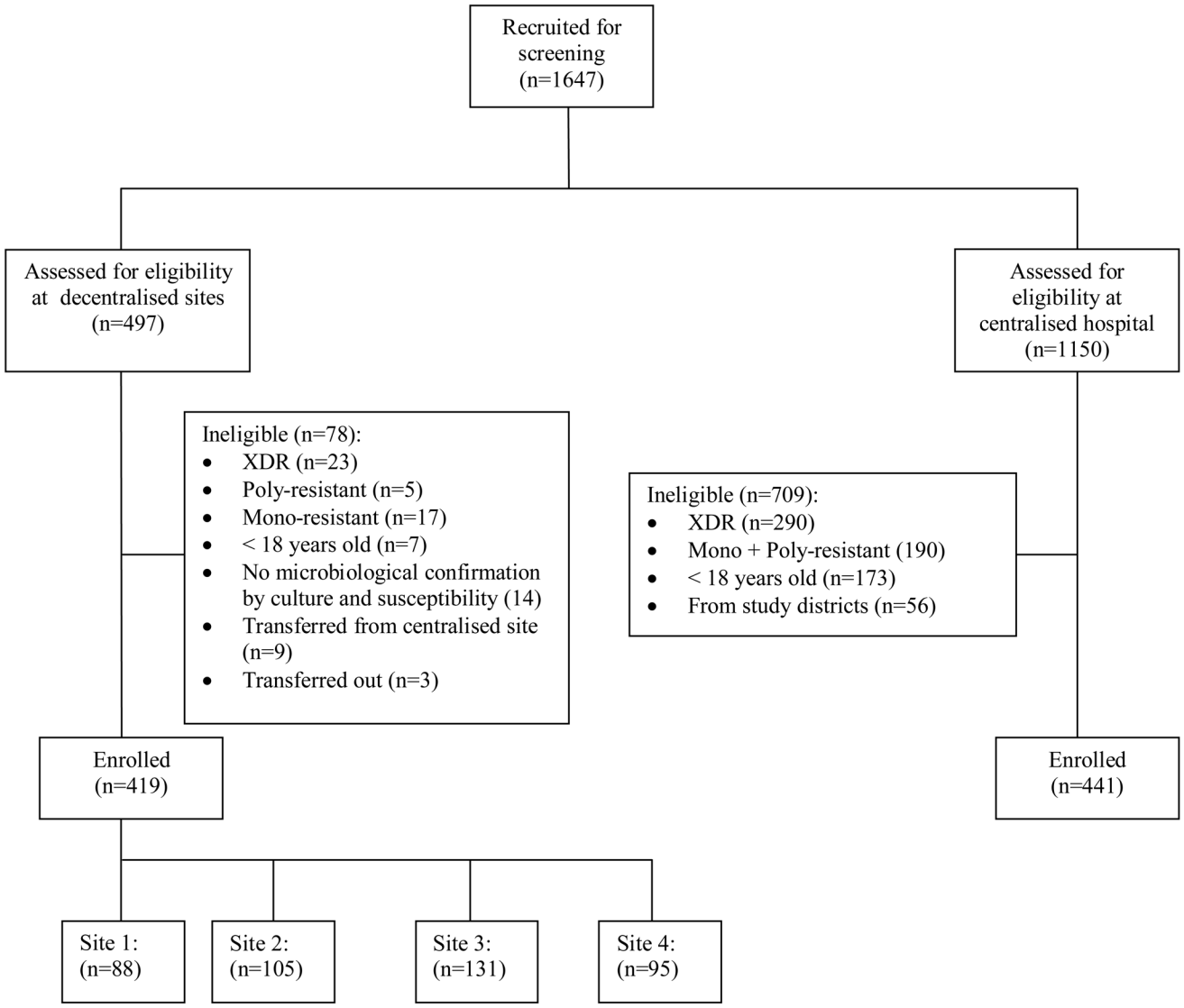
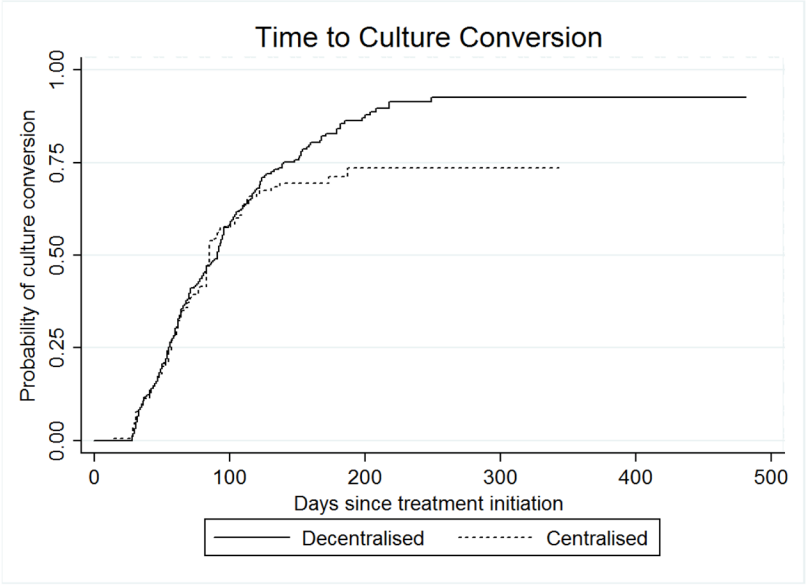


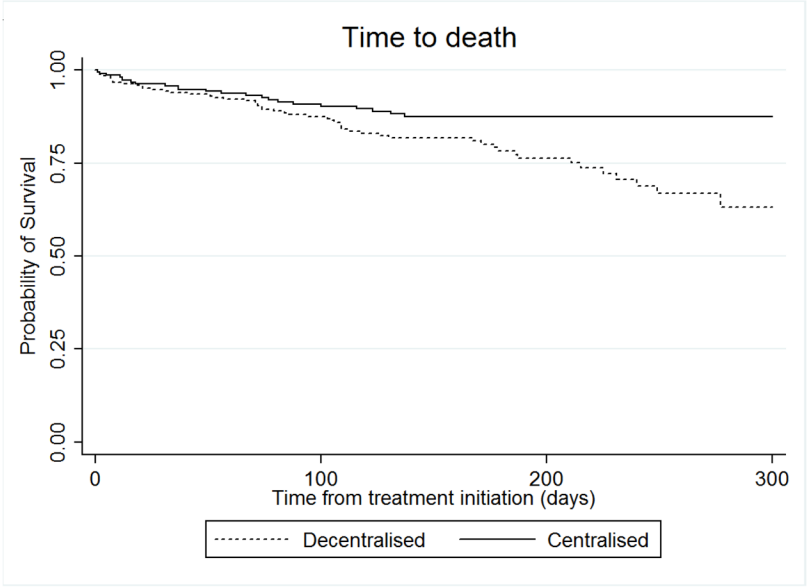
Figure II.
Schema of enrolment



P-value =0.171

Figure III.

Comparison of the time to culture conversion in MDR-TB patients treated at a centralised hospital and decentralised sites, 1 June 2008–30 November 2009



P-value = 0.095

Figure IV.
Comparison of the time to death in MDR-TB patients treated at a centralised hospital and decentralised sites, 1 June 2008–30 November 2009

Table I

Baseline characteristics of study population

		Centralised hospital	Decentralised Sites					
			All decentralised sites	Site 1	Site 2	Site 3	Site 4	P-values
Patients enrolled per site (N)		441	419	88	105	131	95	
Sex:Female, n (%)		229 (52)	205 (49)	-	-	-	-	0.459
				52 (59)	60 (57)	58 (44)	35 (37)	0.002
Mean age, years: n (Range), 95%CI		35.2 (18 – 79) 34 – 36	36.3 (18 – 80) 35 – 37	-	-	-	-	0.140
				35 (18 – 60) 33–38	38 (18 – 80) 35 – 41	34 (18 – 56) 32 – 35	39 (18 – 70) 36 – 41	0.002
HIV status	HIV positive: n (%)	337 (79)	274 (75)	-	-	-	-	0.306
				64 (73)	69 (66)	70 (54)	71 (75)	0.047
	HIV unknown: n (%)	16 (4)	52 (12)	-	-	-	-	
				6 (7)	12 (11)	24 (18)	10 (10)	
HIV positive patients on ART: n (%)		N=337 171 (51)	N=274 172 (63)	-	-	-	-	<0.001
				N=64 49 (77)	N=69 54 (78)	N=70 45 (64)	N=71 24 (34)	<0.001

Centralised hospital: Initial hospitalisation and ongoing care at a centralised specialist hospital.

Decentralised sites: Initial hospitalisation and ongoing care at a district hospital and in the community. CI: Confidence interval

Table II

Tuberculosis characteristics of study population

		Centralised Hospital	Decentralised Sites					P-values
			All decentralised sites	Site 1	Site 2	Site 3	Site 4	
Patients enrolled per site (N)		441	419	88	105	131	95	
Sputum smear positive: n (%)		240 (54)	305 (73)	-	-	-	-	<0.001
		-	-	56 (64)	72 (69)	101 (77)	76 (80)	0.039
Extrapulmonary TB: n (%)		1 (0.2)	4 (1)	-	-	-	-	0.164
		-	-	0	3 (3)	1 (1)	0	0.170
Previous TB Treatment: n (%)		423 (96)	252 (60)	-	-	-	-	<0.001
		-	-	65 (74)	51 (49)	95 (72)	41 (43)	0.395
Number of patients resistant to:	2 drugs: n (%)	183 (42)	177 (42)	-	-	-	-	0.824
		-	-	36 (41)	39 (37)	58 (44)	44 (46)	0.564
	> 2 drugs: n (%)	258 (58)	242 (58)	-	-	-	-	
		-	-	52 (59)	66 (63)	73 (56)	51 (54)	
Number of patients in injectable phase on:	< 6 drugs: n (%)	N=436 105 (24)	N=413 157 (38)	-	-	-	-	<0.001
		-	-	N=87 9 (10)	N=100 28 (28)	N=131 111 (85)	N=95 9 (9)	<0.001
	≥ 6 drugs: n (%)	N=436 331 (76)	N=413 256 (62)	-	-	-	-	
		-	-	78 (90)	72 (72)	20 (15)	86 (91)	
Median time to MDR-TB treatment initiation, days: n (IQR)		N=423 93 (71–120)	N=406 72 (56–99)	-	-	-	-	<0.001
		-	-	N=87 68 (50–93)	N=95 70 (50–94)	N=129 70 (54–97)	N=95 83 (64–120)	<0.001

Injectable phase: Initial phase of MDR-TB treatment which includes an injectable.

CI: Confidence interval

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Table III

Treatment outcomes

	Centralised Hospital	Decentralised Sites				
		All decentralised sites	Site 1	Site 2	Site 3	Site 4
Patients enrolled per site (N)	441	419	88	105	131	95
Died	30 (7%)	67 (16%)	7(8%)	15 (14%)	18 (14%)	27 (28%)
Failed	0	15 (4%)	3 (3%)	7 (7%)	4 (3%)	1 (1%)
Defaulted	7 (2%)	14 (3%)	0	4 (4%)	8 (6%)	2 (2%)
Total “unsuccessful Rx outcomes”	37 (8%)	96 (23%)	10 (12%)	26 (25%)	30 (23%)	30 (32%)
Lost to follow up	126 (29%)	65 (15%)	32 (36%)	3 (3%)	27 (21%)	74 (56%)
Still on treatment	278 (63%)	258 (62%)	46 (52%)	76 (72%)	3 (3%)	62 (65%)

Rx = treatment