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Successful expansion of community-based drug-resistant TB care in rural Eswatini – a retrospective cohort study

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Abstract

OBJECTIVES Provision of drug-resistant tuberculosis (DR-TB) treatment is scarce in resource-limited settings. We assessed the feasibility of ambulatory DR-TB care for treatment expansion in rural Eswatini.

METHODS Retrospective patient-level data were used to evaluate ambulatory DR-TB treatment provision in rural Shiselweni (Eswatini), from 2008 to 2016. DR-TB care was either clinic-based led by nurses or community-based at the patient's home with involvement of community treatment supporters for provision of treatment to patients with difficulties in accessing facilities. We describe programmatic outcomes and used multivariate flexible parametric survival models to assess time to adverse outcomes. Both care models were costed in supplementary analyses.

RESULTS Of 698 patients initiated on DR-TB treatment, 57% were women and 84% were HIV-positive. Treatment initiations increased from 27 in 2008 to 127 in 2011 and decreased thereafter to 51 in 2016. Proportionally, community-based care increased from 19% in 2009 to 77% in 2016. Treatment success was higher for community-based care (79%) than clinic-based care (68%, $P = 0.002$). After adjustment for covariate factors among adults ($n = 552$), the risk of adverse outcomes (death, loss to follow-up, treatment failure) in community-based care was reduced by 41% (adjusted hazard ratio 0.59, 95% CI: 0.39–0.91). Findings were supported by sensitivity analyses. The care provider's per-patient costs for community-based (USD13 345) and clinic-based (USD12 990) care were similar.

CONCLUSIONS Ambulatory treatment outcomes were good, and community-based care achieved better treatment outcomes than clinic-based care at comparable costs. Contextualised DR-TB care programmes are feasible and can support treatment expansion in rural settings.

keywords Eswatini, drug resistance TB, community, ambulatory

Introduction

The drug-resistant tuberculosis (DR-TB) epidemic is a global public health crisis with a huge diagnosis and treatment gap in resource-limited settings (RLS) [1]. Of an estimated 90 000 DR-TB cases in Africa in 2017, approximately 30% were laboratory diagnosed and about 21% received DR-TB treatment, with treatment success rates remaining below 70% [1]. More than 50% of TB cases are co-infected with HIV in Southern Africa, and HIV is a significant contributor to mortality in DR-TB patients [1–3].

Previously, many countries used centralised programmatic approaches (e.g. hospitalisation) to facilitate provision of DR-TB care and antiretroviral therapy (ART) for patients co-infected with HIV [4–6]. However, hospitalisation generated bottlenecks for treatment scale-up in RLS, including prolonged time to diagnosis, high pre-treatment mortality and increased transmission of TB at general hospitals [7–9]. The mismatch of needs and realities on the ground prompted WHO to recommend ambulatory DR-TB care in 2011 [10]. In ambulatory care, patients receive DR-TB care as outpatients during their entire treatment, irrespective of culture and smear status.

It is either clinic-based, which requires patients to travel daily to the facility for directly observed therapy (DOT), or community-based with health professionals (e.g. nurses) or community treatment supporters (CTS) providing care at a venue in the community. Both approaches appear to be feasible in low- and high-HIV prevalence settings [4,11–17], and they have the potential to increase case detection, shorten time to treatment initiation and improve survival [14].

Specific settings may require a combination of care models [18]. Operationalisation should be informed by the epidemiological profile (DR-TB and HIV burden), the setting (rural *vs.* urban), health policies (e.g. task shifting, legal framework) and programmatic factors (e.g. availability of human resources for health, decentralisation capacity). Médecins Sans Frontières (MSF), with support from the Ministry of Health (MOH) of Eswatini (formerly Swaziland), established an ambulatory DR-TB care programme in the Shiselweni region in 2008. This programme increasingly relied on community-based care with involvement of CTS to expand programmatic reach into rural areas. Here, we describe two differentiated care models (community *vs.* clinic), their programmatic feasibility under routine conditions and treatment outcomes in order to draw lessons to inform health policy.

Methods

Setting

Eswatini has an HIV prevalence of 32% in 18–49-year-olds [19]. The TB incidence was the highest in the world in 2007 (1198 cases per 100 000 population) and decreased to 308 cases per 100 000 population in 2017 [1,20], of which 8% and 34% of new and re-treatment cases had multidrug-resistant TB [21]. The rural Shiselweni region in the south had approximately 204 000 inhabitants in 2017, with a population density ranging from 25 to 106 people per square kilometre [22]. It also had the lowest density of treatment facilities, inpatient beds and health workers in the country [23,24]. In 2008, MSF, in collaboration with the MOH, initiated a DR-TB care decentralisation project allowing for clinic-based DR-TB care. In 2009, MSF added a community-based care intervention for patients with barriers to accessing the nearest facility.

DR-TB treatment. Medical doctors initiated standardised DR-TB treatment regimens in three secondary care inpatient and outpatient facilities in Shiselweni. Empirical DR-TB treatment initiation was permitted for high-risk presumptive DR-TB cases based on clinical criteria. Access to culture-based drug susceptibility testing (DST) was rare; the MTBDRplus line probe assay was not routinely available, and the Xpert MTB/RIF assay was introduced in November 2011. Clinically, severe DR-TB cases were hospitalised between the years 2008 and 2011. Thereafter, hospitalisation in the newly established regional TB ward at the time of treatment initiation for up to 2 weeks was recommended for all patients to allow enough time for infection control measures to be put in place at the patient's home. The intensive phase for DR-TB treatment lasted 8 months and the continuation phase at least 12 months. Treatment regimens were modified according to subsequent DST results, where available. Patients with HIV co-infection were eligible for antiretroviral therapy.

DR-TB care models. Table S1 summarises programmatic features of the clinic-based and community-based care models. Standardised protocols defined eligibility for community-based care based on geographical access constraints (living more than 5 km away from the nearest facility) and socio-economic criteria (old age, disability, insufficient transport money for daily travel to the clinic, being the only caretaker of children at home). Clinical presentation was not a selection criterion. The CTS – a lay person without medical expertise and who was not a family or household member – was identified by the patient and the community DR-TB nurse and needed to live in the patient's neighbourhood. The CTS received daily training by the MSF community DR-TB nurse during the first 2 weeks of treatment. Thereafter, the CTS provided daily DOT and intramuscular injectables at the patient's home. In addition, mobile DR-TB teams consisting of the DR-TB nurse and a driver visited patients' homes for supervision of the CTS at least twice monthly and whenever the need arose. The CTS was compensated (40 USD per month) for the entire intensive phase. Thereafter, CTS support ceased and family members provided DOT during the continuation phase.

In clinic-based care, patients went daily to the nearest health facility for nurse-supervised morning DOT and intramuscular injection. All patients had a family treatment supporter for evening dose DOT. The DR-TB community nurse also visited the patient's home, although this was less frequent (once a month) and briefer in duration than in community-based care.

Patients could transition between care models if their life circumstances changed, or could receive injectable treatment between monthly drug refills outside the region (mixed care model).

In all care models, patients visited the secondary facilities for once-monthly clinical and laboratory monitoring,

drug refills and patient support groups. Community adherence counsellors and the community nurse traced patients who missed injections or monthly drug refills.

Study design and definitions

We analysed a retrospectively established cohort of patients starting presumptive or DST-confirmed DR-TB treatment in Shiselweni, from January 2008 to December 2016. Data were obtained from a routine electronic DR-TB database used for programmatic monitoring. A DR-TB case was defined as resistance to rifampicin and/or isoniazid, either measured or presumed by the clinician. Thus, we also included patients presenting with isoniazid mono-resistance. Participants were removed from analysis if they were transferred in or if the DST result indicated first-line TB drug sensitivity against both rifampicin and isoniazid. Follow-up was from treatment initiation until the first of a composite unfavourable outcome [death, loss to follow-up (LTFU), clinically or DST-confirmed treatment failure], transfer out of the region or treatment success. LTFU was defined as at least 2 months without a clinic visit. A new DR-TB case was defined as a patient without previous exposure to first- and second-line TB drug treatment. Outcome definitions were based on 2013 WHO recommendations and are provided in detail in Table S2 [25].

Analyses and statistics

Analyses were performed with Stata version 14.01 (College Station, TX, USA). Firstly, patient characteristics at DR-TB treatment initiation and outcomes were described by calendar year and differences were assessed with Pearson's chi-squared test. The mid-year annual nurse-to-patient ratio was calculated by dividing the number of active patients by the number of DR-TB community nurses.

Secondly, we used multiple imputation by chained equation to predict missing data as a function of baseline covariate data [26]. Twenty imputed datasets were created. The proportional hazards assumption was assessed with Schoenfeld residual statistics. Then, we used covariate-adjusted flexible parametric survival models (Royston–Parmar models) [27,28] to describe associations of baseline factors in the entire cohort with time to the composite unfavourable outcome. Observations were censored in case of transfer out and treatment success.

Thirdly, we describe predictors of enrolment into clinic-based *vs*. community-based care for patients aged ≥16 years and compare their treatment outcomes. Because standard procedures permitted hospitalisation for 2 weeks at treatment initiation and early patient outcomes were likely to be associated with disease progression and factors other than exposure to the intervention, follow-up time started from 15 days after treatment initiation. Covariates for inclusion into analyses were determined *a priori* with directed acyclic graphs (DAGs) [29]. Multivariate logistic regression analysis was used to describe predictors of community-based care. Then, we used the Royston–Parmar models to assess the association of community-based care with the outcome and plotted standardised failure functions and difference in hazard functions based on the fitted model [30]. In sensitivity analyses (SA), follow-up time started at 8 days (SA-1) or 22 days (SA-2) after DR-TB treatment initiation. SA-3 included the nurse-to-patient ratio as an additional covariate, SA-4 used inverse probability weighting [31] to estimate the association with the outcome, and SA-5 assessed time to death while all other outcomes were censored.

In a supplementary analysis, we evaluated affordability of community-based care from the health systems perspective for the years 2012–2013 with USD converted to 2013 levels. A normative costing approach was chosen, and assumptions were developed through field visits and close consultations with implementers, while some costs were supplemented with 2012 historical data used for a previous HIV decentralised costing exercise (unpublished data). Cost categories included human resources, transport, drugs, laboratory tests, incentives, HIV treatment and other costs such as hospitalisation, which were calculated per person over a 24-month treatment period. DR-TB drugs, laboratory, and HIV-related costs were assumed to be the same for both care models.

Ethics

This retrospective analysis was approved by the Ministry of Health and the Social Welfare Scientific Ethics Committee of Eswatini. This research fulfilled the exemption criteria set by the MSF Ethics Review Board (ERB) for *a posteriori* analyses of routinely collected clinical data and thus did not require MSF ERB review. It was conducted with permission from Micaela Serafini (Medical Director, Operational Centre Geneva), MSF.

Results

Programmatic trends and baseline characteristics

A total of 698 patients initiated DR-TB treatment between 2008 and 2016 (Table 1). DR-TB initiations increased from 27 in 2008 to 127 in 2011 and decreased thereafter to 51 in 2016. Proportionally, community-based care increased from 18.8% in 2009 to 76.5% in

Table 1 Annual trends in DR-TB treatment initiations (*n*, %) in Shiselweni (Eswatini), from January 2008 to December 2016

	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Total	27	80	99	127	105	68	76	65	51	698
Care model										
Clinic	27 (100.0)	60 (75.0)	62 (62.6)	70 (55.1)	59 (56.2)	26 (38.2)	14 (18.4)	9 (13.8)	2 (3.9)	329 (47.1)
Community	0 (0.0)	15 (18.8)	29 (29.3)	39 (30.7)	44 (41.9)	37 (54.4)	56 (73.7)	48 (73.8)	39 (76.5)	307 (44.0)
Mixed	0 (0.0)	5 (6.3)	8 (8.1)	18 (14.2)	2 (1.9)	5 (7.4)	6 (7.9)	8 (12.3)	10 (19.6)	62 (8.9)
Health cluster										
Nhlangano	13 (48.1)	36 (45.0)	40 (40.4)	57 (44.9)	47 (44.8)	29 (42.6)	28 (36.8)	24 (36.9)	19 (37.3)	293 (42.0)
Hlathikulu	8 (29.6)	30 (37.5)	46 (46.5)	49 (38.6)	31 (29.5)	13 (19.1)	24 (31.6)	19 (29.2)	12 (23.5)	232 (33.2)
Matsanjeni	6 (22.2)	14 (17.5)	13 (13.1)	21 (16.5)	27 (25.7)	26 (38.2)	24 (31.6)	22 (33.8)	20 (39.2)	173 (24.8)
Sex										
Women	24 (88.9)	50 (62.5)	61 (61.6)	73 (57.5)	58 (55.2)	38 (55.9)	45 (59.2)	24 (36.9)	26 (51.0)	399 (57.2)
Men	3 (11.1)	30 (37.5)	38 (38.4)	54 (42.5)	47 (44.8)	30 (44.1)	31 (40.8)	41 (63.1)	25 (49.0)	299 (42.8)
Age, years										
0–15	0 (0.0)	6 (7.5)	13 (13.1)	14 (11.0)	6 (5.7)	5 (7.4)	5 (6.6)	0 (0.0)	3 (5.9)	52 (7.4)
16–24	2 (7.4)	10 (12.5)	14 (14.1)	17 (13.4)	13 (12.4)	8 (11.8)	9 (11.8)	8 (12.3)	5 (9.8)	86 (12.3)
25–49	22 (81.5)	53 (66.3)	60 (60.6)	81 (63.8)	76 (72.4)	47 (69.1)	47 (61.8)	46 (70.8)	37 (72.5)	469 (67.2)
≥50	3 (11.1)	11 (13.8)	12 (12.1)	15 (11.8)	10 (9.5)	8 (11.8)	15 (19.7)	11 (16.9)	6 (11.8)	91 (13.0)
BMI (*n* = 81, 11.6%)*										
<18.5	13 (48.1)	29 (42.0)	32 (39.0)	43 (40.6)	23 (24.0)	17 (28.3)	28 (40.0)	25 (41.7)	15 (31.9)	225 (36.5)
18.5–24.9	10 (37.0)	31 (44.9)	40 (48.8)	54 (50.9)	66 (68.8)	34 (56.7)	39 (55.7)	31 (51.7)	26 (55.3)	331 (53.6)
≥25	4 (14.8)	9 (13.0)	10 (12.2)	9 (8.5)	7 (7.3)	9 (15.0)	3 (4.3)	4 (6.7)	6 (12.8)	61 (9.9)
Treatment history										
New case	1 (3.7)	6 (7.5)	9 (9.1)	20 (15.7)	56 (53.3)	47 (69.1)	54 (71.1)	56 (86.2)	46 (90.2)	295 (42.3)
Previous 1st line	25 (92.6)	67 (83.8)	86 (86.9)	100 (78.7)	44 (41.9)	17 (25.0)	22 (28.9)	6 (9.2)	5 (9.8)	372 (53.3)
Previous 2nd line	1 (3.7)	7 (8.8)	4 (4.0)	7 (5.5)	5 (4.8)	4 (5.9)	0 (0.0)	3 (4.6)	0 (0.0)	31 (4.4)
TB site										
Pulmonary	26 (96.3)	76 (95.0)	94 (94.9)	125 (98.4)	95 (90.5)	65 (95.6)	75 (98.7)	64 (98.5)	51 (100.0)	671 (96.1)
Extrapulmonary	1 (3.7)	4 (5.0)	5 (5.1)	2 (1.6)	10 (9.5)	3 (4.4)	1 (1.3)	1 (1.5)	0 (0.0)	27 (3.9)
Smear status (*n* = 161, 23.1%)*										
Negative	3 (14.3)	8 (13.1)	21 (29.2)	24 (24.7)	30 (31.9)	9 (25.0)	27 (43.5)	8 (15.4)	6 (14.3)	136 (25.3)
Scanty/smear+	3 (14.3)	18 (29.5)	17 (23.6)	33 (34.0)	33 (35.1)	11 (30.6)	11 (17.7)	20 (38.5)	26 (61.9)	172 (32.0)
Smear++	2 (9.5)	13 (21.3)	11 (15.3)	14 (14.4)	11 (11.7)	6 (16.7)	10 (16.1)	5 (9.6)	3 (7.1)	75 (14.0)
Smear+++	13 (61.9)	22 (36.1)	23 (31.9)	26 (26.8)	20 (21.3)	10 (27.8)	14 (22.6)	19 (36.5)	7 (16.7)	154 (28.7)
DR-TB type										
RIF & INH resistance	14 (51.9)	51 (63.8)	52 (52.5)	44 (34.6)	23 (21.9)	1 (1.5)	19 (25.0)	19 (29.2)	15 (29.4)	238 (34.1)
RIF mono-resistance	1 (3.7)	1 (1.3)	10 (10.1)	16 (12.6)	58 (55.2)	17 (25.0)	37 (48.7)	35 (53.8)	16 (31.4)	191 (27.4)
INH mono-resistance	7 (25.9)	16 (20.0)	24 (24.2)	31 (24.4)	7 (6.7)	0 (0.0)	16 (21.1)	7 (10.8)	12 (23.5)	120 (17.2)
Empirical	5 (18.5)	12 (15.0)	13 (13.1)	36 (28.3)	17 (16.2)	50 (73.5)	4 (5.3)	4 (6.2)	8 (15.7)	149 (21.3)

Table 1 (*Continued*)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
HIV/ART/CD4 status (n = 29, 4.2%)*										
HIV-negative	6 (23.1)	21 (26.9)	12 (12.4)	25 (20.3)	13 (12.5)	19 (30.2)	18 (25.4)	14 (23.7)	14 (29.2)	142 (21.2)
HIV+ on ART, CD4 ≤ 200 cells/mm^3	4 (15.4)	21 (26.9)	35 (36.1)	45 (36.6)	39 (37.5)	21 (33.3)	22 (31.0)	11 (18.6)	16 (33.3)	214 (32.0)
HIV+ on ART, CD4 > 200 cells/mm^3	8 (30.8)	22 (28.2)	32 (33.0)	31 (25.2)	21 (20.2)	14 (22.2)	16 (22.5)	22 (37.3)	10 (20.8)	176 (26.3)
HIV+ without ART, CD4 ≤ 200 cells/mm^3	2 (7.7)	6 (7.7)	6 (6.2)	13 (10.6)	18 (17.3)	7 (11.1)	8 (11.3)	7 (11.9)	5 (10.4)	72 (10.8)
HIV+ without ART, CD4 > 200 cells/mm^3	6 (23.1)	8 (10.3)	12 (12.4)	9 (7.3)	13 (12.5)	2 (3.2)	7 (9.9)	5 (8.5)	3 (6.3)	65 (9.7)
Nurse-to-patient ratio†										
Clinic	–	46	37.5	46	26.3	22.3	7.3	4.7	3	
Community	–	9	11.5	17.5	20.3	21	19	27.3	24.7	
Total	–	56	52.5	75	52	44.3	27.7	32.7	29	

%, percentage; ART, antiretroviral therapy; BMI, body mass index; DR-TB, drug-resistant tuberculosis; INH, isoniazid; n, number; RIF, rifampicin.
*Number and percentage of missing values.
†This is the ratio of one community DR-TB nurse to patients active on DR-TB treatment followed in community-based and clinic-based care and does not include facility-based nurses. In both care models, the community TB nurse visited the patients' homes. The frequency of home visits and the time spent with patients in the community-based care model was approximately twice the time and frequency for patients in the clinic-based care model.

2016, with a reciprocal decrease in clinic-based care, while the mixed care model accounted for 8.9% (n = 62) of all cases (Figure 1a). The active mid-year treatment cohort increased from 13 cases in 2008 to 156 cases in 2012, with a decrease thereafter reaching 87 cases in 2016 (Figure 1b). At the same time, the community DR-TB nurse-to-patient ratio for the active treatment cohort decreased for clinic-based care from 46 in 2009 to 3 in 2016 and increased for community-based care from 9 to 24.7, respectively (Figure 1b).

Most patients (n = 405, 58%) initiated treatment at the more rural health clusters of Hlathikulu and Matsanjeni. Most patients were women (57.2%), and 12.3% and 67.2% were aged 16–24 and 25–49 years. The proportion of new DR-TB patients increased from 3.7% in 2008 to 90.2% in 2016 (Figure 1c), with most (96.1%) of them being pulmonary TB cases and 25.3% being sputum smear-negative. Overall, 21.3% of patients initiated DR-TB treatment empirically (Figure 1d). Of 669 (95.8%) patients with recorded HIV/ART/CD4 status, 78.8% were co-infected with HIV, 58.3% received ART before DR-TB treatment initiation, and the median CD4 cell count was 172 [interquartile range (IQR): 76–322] cells/mm^3.

Programmatic outcomes

Overall treatment success was 71.6%. It was higher for community-based care (78.8%) than clinic-based (68.1%, P = 0.002) and mixed (54.8%, P < 0.001) care (Figure 2, Table 2). Overall, LTFU was 5.0%, and treatment failure was 1.9% and was comparable between community-based and clinic-based care models. Overall mortality was 19.8%, being lower in community-based care (13.7%) than in clinic-based care (23.4%, P = 0.002).

In multivariate analysis (Table 3), the risk of an adverse outcome was reduced by 36% [adjusted hazard ratio (aHR) 0.64, 95% confidence interval (CI): 0.43–0.97] and 40% (aHR 0.60, 95% CI: 0.36–1.00) for the calendar years 2011–2013 and 2014–2016 when compared with 2008–2010, as well as by 37% (aHR 0.63, 95% CI: 0.43–0.93) for patients with previous first-line TB drug exposure (*vs.* new DR-TB cases). The risk was increased by 75% (aHR 1.75, 95% CI: 1.16–2.65) for patients initiating empirical DR-TB therapy, while no associations were detected for other factors.

Predictors and outcomes of care model

We removed 146 (20.9%) patients from further analyses. They initiated DR-TB treatment before community-based

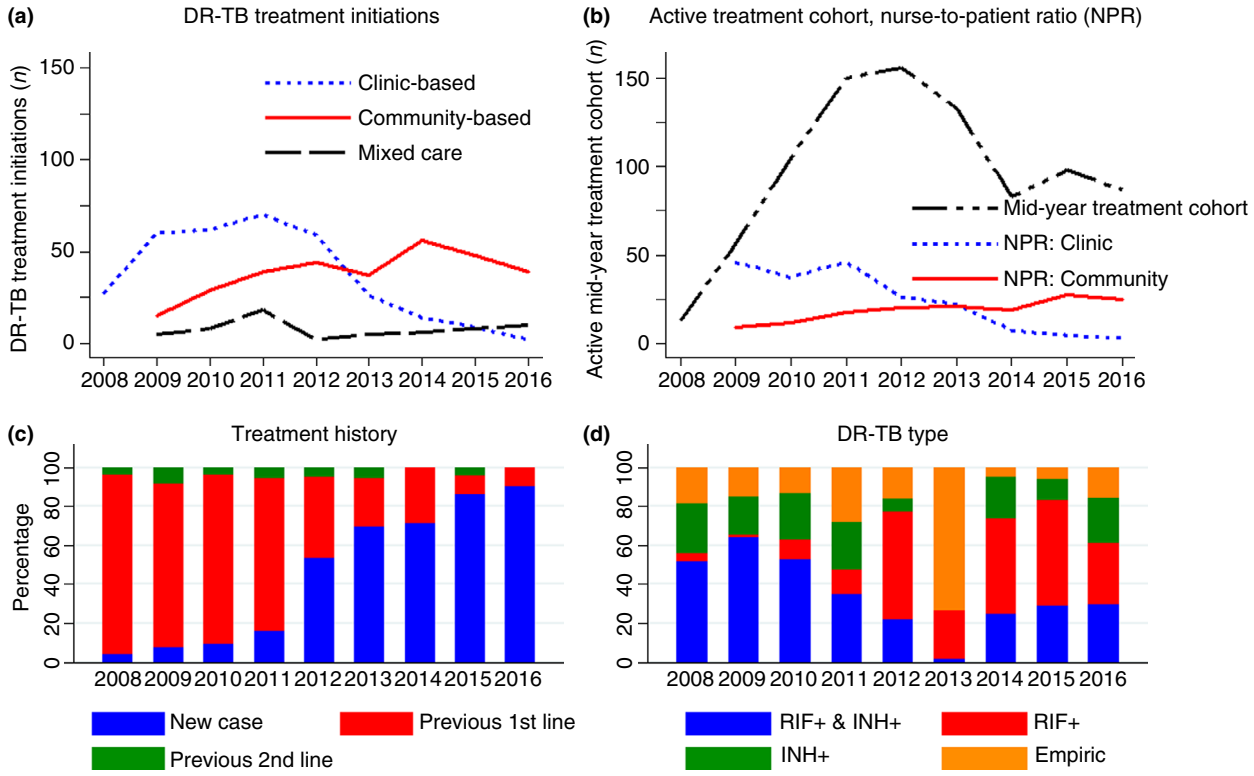


Figure 1 Main temporal trends in DR-TB treatment cases in Shiselweni (Eswatini), from January 2008 to December 2016. DR-TB, drug-resistant tuberculosis; NPR, nurse-to-patient ratio; RIF+, rifampicin resistance; INH+, isoniazid resistance. [Colour figure can be viewed at wileyonlinelibrary.com].

care became available in 2009, had a negative treatment outcome within 14 days of treatment initiation and thus before they could be allocated to either care model, or were ineligible for community-based care as they were younger than 16 years. The remaining 552 patients were more likely to be enrolled into community-based care in the later programmatic periods, in the more rural health clusters, if they were new TB cases (55.6% *vs.* 32.1%) and if they had rifampicin mono-resistance (36.6% *vs.* 23.1%; Table 4). In multivariate analysis, the odds of enrolment into community-based care were increased for later programmatic periods (*vs.* 2009–2010) and the more rural health clusters, while it was decreased for men and patients with body mass index (BMI) > 25 (*vs.* BMI < 18.5; Table 4).

Total follow-up time was 770.2 years, with a median of 1.6 and 1.7 years for clinic-based and community-based care. A total of 77/268 (28.7%) and 19/284 (20.1%) patients had an adverse outcome (death, LTFU, treatment failure), respectively. After adjustment for covariate factors, risk of an adverse outcome was 41% lower (aHR 0.59, 95% CI: 0.39–0.91) for community-based care (Table 4). The cumulative hazard is displayed in Figure 3. The effect varied by duration of treatment, with community-based care having a decreased hazard of an unfavourable outcome during the first 9 months of treatment and a similar hazard thereafter (Figure 3).

Sensitivity analyses (SA-1 to SA-4) confirmed the findings, with overall risk reduction for community-based care and aHRs ranging from 0.56 to 0.64 (Table S3). The analysis considering mortality as the outcome (SA-5) showed a risk reduction of 48% (aHR 0.52, 95% CI: 0.31–0.86).

Programme costs

The total costs of the community-based and clinic-based care were almost equivalent, at, respectively, USD13 345 and USD12 990 per patient for 24 months of DR-TB treatment (Figure 4, Table S4). The estimated 8-month intensive phase accounted for about 52% of the total costs of the 24 months' treatment for both models.

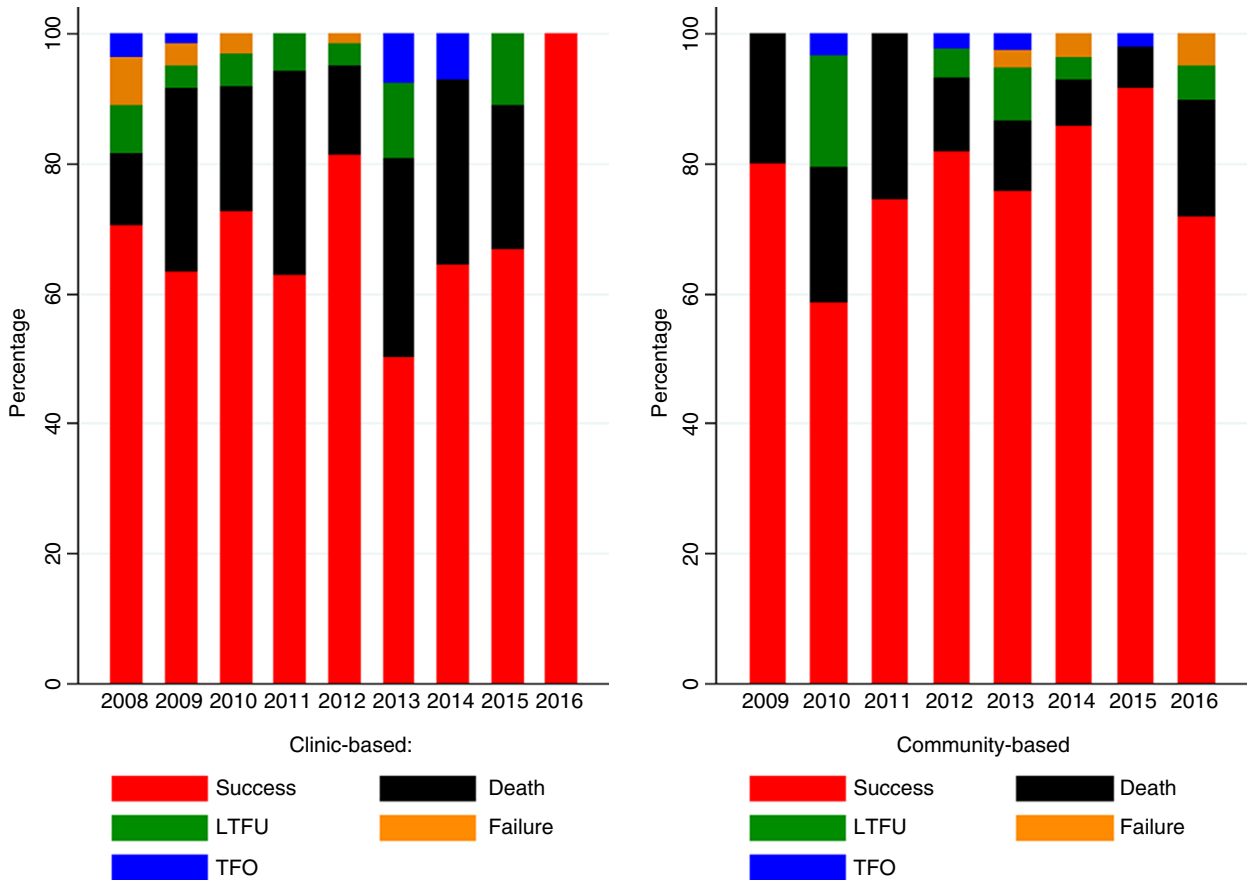


Figure 2 Main temporal trends in DR-TB treatment outcomes in Shiselweni (Eswatini), from January 2008 to December 2016. LTFU, loss to follow-up; TFO, transfer out. There was no community-based care in 2008. Only two patients were evaluated for treatment outcomes in clinic-based care in 2016. [Colour figure can be viewed at wileyonlinelibrary.com].

Incentives and enablers for patients, CTS and family treatment supporters accounted for USD1497 (11%) and USD1242 (10%), respectively. The main cost drivers in both care models were DR-TB drugs (34–35%), laboratory tests (20–21%) and human resources (12–13%).

Discussion

We describe an ambulatory care programme which used both clinic-based and community-based care approaches. Community-based care was expanded over time and achieved apparently better programmatic outcomes than clinic-based care (78.8% *vs.* 68.1%) at comparable cost. Multivariate analyses confirmed the findings, with community-based care reducing the overall hazard of an unfavourable outcome by 41%. Notably, the rate of the outcome varied by duration of treatment, with benefits seen only during the first 9 months of follow-up (intensive care phase). The intensive phase coincided with CTS support, which, however, ceased thereafter.

Findings in context

This study supports existing evidence on the feasibility of ambulatory care models [15]. Overall, treatment success was 71.6% in a predominantly HIV-infected DR-TB treatment cohort and comparable to outcomes reported internationally (65% treatment success in multidrug-resistant and extensively drug-resistant TB) [32]. Predictors of treatment outcomes vary by setting and include clinical, demographic and social factors [13,14,16,33–35]. In this study, only a few factors were associated with adverse outcomes (empirical DR-TB treatment, treatment history, temporal trends).

In our setting, treatment success in community-based care was better than in clinic-based care. The good

Table 2 Annual trends in programmatic treatment outcomes (*n*, %) of DR-TB treatment cases in Shiselweni (Eswatini), from January 2008 to December 2016

	2008 *n* (%)	2009 *n* (%)	2010 *n* (%)	2011 *n* (%)	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	2016 *n* (%)	Total *n* (%)
All cases*										
Success†	19 (70.4)	53 (66.3)	69 (69.7)	86 (67.7)	84 (80)	44 (64.7)	57 (75)	51 (78.5)	37 (72.6)	500 (71.6)
Completed	4 (14.8)	15 (18.8)	17 (17.2)	26 (20.5)	13 (12.4)	9 (13.2)	4 (5.3)	5 (7.7)	3 (5.9)	96 (13.8)
Cured	15 (55.6)	38 (47.5)	52 (52.5)	60 (47.2)	71 (67.6)	34 (50.0)	53 (69.7)	46 (70.8)	34 (66.7)	403 (57.7)
LTFU	2 (7.4)	3 (3.8)	8 (8.1)	5 (3.9)	5 (4.8)	7 (10.3)	2 (2.6)	1 (1.5)	2 (3.9)	35 (5.0)
Death	3 (11.1)	20 (25.0)	19 (19.2)	33 (26.0)	13 (12.4)	14 (20.6)	14 (18.4)	12 (18.5)	10 (19.6)	138 (19.8)
Failure	2 (7.4)	2 (2.5)	2 (2.0)	1 (0.8)	1 (1.0)	1 (1.5)	2 (2.6)	0 (0.0)	2 (3.9)	13 (1.9)
TFO	1 (3.7)	2 (2.5)	1 (1.0)	2 (1.6)	2 (1.9)	3 (4.4)	1 (1.3)	1 (1.5)	0 (0.0)	13 (1.9)
Clinic										
Success†	19 (70.4)	38 (63.3)	45 (72.6)	44 (62.9)	48 (81.4)	13 (50)	9 (64.3)	6 (66.7)	2 (100)	224 (68.1)
Completed	4 (14.8)	12 (20.0)	13 (21.0)	13 (18.6)	8 (13.6)	5 (19.2)	1 (7.1)	0 (0.0)	0 (0.0)	56 (17.0)
Cured	15 (55.6)	26 (43.3)	32 (51.6)	31 (44.3)	40 (67.8)	7 (26.9)	8 (57.1)	6 (66.7)	2 (100.0)	167 (50.8)
LTFU	2 (7.4)	2 (3.3)	3 (4.8)	4 (5.7)	2 (3.4)	3 (11.5)	0 (0.0)	1 (11.1)	0 (0.0)	17 (5.2)
Death	3 (11.1)	17 (28.3)	12 (19.4)	22 (31.4)8 (13.6)	9 (34.6)	4 (28.6)	2 (22.2)	0 (0.0)	77 (23.4)	
Failure	2 (7.4)	2 (3.3)	2 (3.2)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.1)
TFO	1 (3.7)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	1 (7.1)	0 (0.0)	0 (0.0)	5 (1.5)
Community										
Success†	–	12 (80)	17 (58.6)	29 (74.4)	36 (81.8)	28 (75.7)	48 (85.7)	44 (91.7)	28 (71.8)	242 (78.8)
Completed	–	2 (13.3)	3 (10.3)	7 (17.9)	5 (11.4)	4 (10.8)	3 (5.4)	4 (8.3)	2 (5.1)	30 (9.8)
Cured	–	10 (66.7)	14 (48.3)	22 (56.4)	31 (70.5)	24 (64.9)	45 (80.4)	40 (83.3)	26 (66.7)	212 (69.1)
LTFU	–	0 (0.0)	5 (17.2)	0 (0.0)	2 (4.5)	3 (8.1)	2 (3.6)	0 (0.0)	2 (5.1)	14 (4.6)
Death	–	3 (20.0)	6 (20.7)	10 (25.6)	5 (11.4)	4 (10.8)	4 (7.1)	3 (6.3)	7 (17.9)	42 (13.7)
Failure	–	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	2 (3.6)	0 (0.0)	2 (5.1)	5 (1.6)
TFO	–	0 (0.0)	1 (3.4)	0 (0.0)	1 (2.3)	1 (2.7)	0 (0.0)	1 (2.1)	0 (0.0)	4 (1.3)

%, percentage; LTFU, loss to follow-up; *n*, number; TFO, transfer out.
*This combines all patients from community-based, clinic-based and mixed care models.
†Treatment success combines patients who were cured and completed treatment.

Table 3 Baseline characteristics and associations with attrition of DR-TB treatment cases (n = 698) in Shiselweni (Eswatini), from January 2008 to December 2016

	Baseline characteristics, n (%)	HR (95% CI)	aHR (95% CI)
Programmatic period			
2008–2010	206 (29.5)	1	1
2011–2013	300 (43.0)	0.94 (0.67–1.31)	0.64 (0.43–0.97)
2014–2016	192 (27.5)	0.81 (0.55–1.19)	0.60 (0.36–1.00)
Health cluster			
Nhlangano	293 (42.0)	1	1
Hlathikulu	232 (33.2)	0.87 (0.61–1.22)	0.92 (0.65–1.32)
Matsanjeni	173 (24.8)	1.10 (0.78–1.57)	1.17 (0.81–1.69)
Sex			
Women	399 (57.2)	1	1
Men	299 (42.8)	0.94 (0.70–1.26)	0.90 (0.66–1.23)
Age, years			
≤15	52 (7.4)	1	1
16–24	86 (12.3)	1.82 (0.85–3.86)	1.92 (0.88–4.19)
25–49	469 (67.2)	1.56 (0.79–3.08)	1.60 (0.79–3.25)
≥50	91 (13.0)	1.68 (0.79–3.61)	2.04 (0.92–4.50)
BMI (n = 81, 11.6%)*			
<18.5	225 (36.5)	1	1
18.5–24.9	331 (53.6)	0.82 (0.59–1.13)	0.85 (0.61–1.19)
≥25	61 (9.9)	0.92 (0.54–1.58)	0.90 (0.51–1.58)
Treatment history			
New case	295 (42.3)	1	1
Previous 1st line	372 (53.3)	0.77 (0.57–1.04)	0.63 (0.43–0.93)
Previous 2nd line	31 (4.4)	1.56 (0.89–2.75)	1.34 (0.71–2.53)
TB site			
Pulmonary	671 (96.1)	1	1
Extrapulmonary	27 (3.9)	1.14 (0.56–2.31)	0.96 (0.46–2.00)
Smear status (n = 161, 23.1%)*			
Negative	136 (25.3)	1	1
Scanty/smear+	172 (32.0)	1.06 (0.64–1.74)	1.06 (0.63–1.77)
Smear++	75 (14.0)	1.24 (0.71–2.14)	1.34 (0.78–2.32)
Smear+++	154 (28.7)	1.15 (0.71–1.85)	1.19 (0.71–1.98)
DR-TB type			
RIF & INH resistance	238 (34.1)	1	1
RIF mono-resistance	191 (27.4)	0.94 (0.64–1.37)	0.99 (0.64–1.52)
INH mono-resistance	120 (17.2)	0.78 (0.49–1.26)	0.86 (0.53–1.41)
Empirical	149 (21.3)	1.57 (1.09–2.26)	1.75 (1.16–2.65)
HIV/ART/CD4 status (n = 29, 4.2%)*			
HIV-negative	142 (21.2)	1	1
HIV+ on ART, CD4 ≤ 200 cells/mm^3	214 (32.0)	1.49 (0.98–2.28)	1.53 (0.97–2.41)
HIV+ on ART, CD4 > 200 cells/mm^3	176 (26.3)	1.01 (0.63–1.61)	1.08 (0.66–1.78)
HIV+ without ART, CD4 ≤ 200 cells/mm^3	72 (10.8)	1.59 (0.94–2.70)	1.66 (0.95–2.93)
HIV+ without ART, CD4 > 200 cells/mm^3	65 (9.7)	0.91 (0.49–1.70)	0.86 (0.45–1.64)

We used multiple imputations in regression analyses for the variables BMI, smear status and HIV/ART/CD4 status. The flexible parametric survival model had two degrees of freedom (one internal knot) and did not have time-dependent covariates.
aHR, adjusted hazard ratio; ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; DR-TB, drug-resistant tuberculosis; HR, hazard ratio; INH, isoniazid; n, number; RIF, rifampicin.
*Number and percentage of missing values.

outcomes may be due to a combination of factors. Firstly, relationships of trust and sustained social contacts between CTS and the family and community may have played a role. Despite emerging evidence of increased acceptability of community-based care models [36], studies on the perception of care provision by CTS are

Table 4 Baseline characteristics, predictors of care model and associations with attrition of DR-TB treatment cases (n = 552) in Shiselweni (Eswatini), from January 2009 to December 2016. Follow-up started at 2 weeks after treatment initiation

	Baseline characteristics			Predictors of care model		Predictors of attrition	
	Clinic, *n* (%)	Community, *n* (%)	*P*-value	OR (95% CI)	aOR (95% CI)	HR (95% CI)	aHR (95% CI)
Care model							
Clinic	268 (100.0)	–		–	–	1	1
Community	–	284 (100.0)		–	–	0.63 (0.44–0.88)	0.59 (0.39–0.91)
Programmatic period							
2009–2010	107 (39.9)	39 (13.7)	<0.001	1	1	1	1
2011–2013	137 (51.1)	108 (38.0)		2.16 (1.39–3.38)	2.43 (1.39–4.24)	0.86 (0.58–1.27)	0.67 (0.41–1.09)
2014–2016	24 (9.0)	137 (48.2)		15.66 (8.88–27.64)	24.65 (11.69–51.95)	0.54 (0.33–0.86)	0.55 (0.28–1.06)
Health cluster							
Nhlangano	145 (54.1)	91 (32.0)	<0.001	1	1	1	1
Hlathikulu	69 (25.7)	102 (35.9)		2.36 (1.57–3.52)	3.28 (2.00–5.39)	0.87 (0.57–1.31)	0.94 (0.61–1.46)
Matsanjeni	54 (20.1)	91 (32.0)		2.69 (1.75–4.11)	2.67 (1.60–4.46)	1.10 (0.74–1.65)	1.32 (0.86–2.04)
Sex							
Women	138 (51.5)	163 (57.4)	0.164	1	1	1	1
Men	130 (48.5)	121 (42.6)		0.79 (0.56–1.10)	0.45 (0.29–0.70)	1.00 (0.71–1.41)	0.96 (0.66–1.40)
Age, years							
16–24	37 (13.8)	41 (14.4)	0.742	1	1	1	1
25–49	191 (71.3)	207 (72.9)		0.98 (0.60–1.59)	1.36 (0.73–2.54)	0.83 (0.53–1.31)	0.95 (0.46–1.95)
≥50	40 (14.9)	36 (12.7)		0.81 (0.43–1.53)	1.15 (0.51–2.58)	0.73 (0.38–1.37)	1.09 (0.62–1.93)
BMI (n = 12, 2.2%)*							
<18.5	85 (32.6)	103 (36.9)	0.336	1	1	1	1
18.5–24.9	145 (55.6)	152 (54.5)		0.87 (0.60–1.25)	0.81 (0.51–1.28)	0.88 (0.60–1.29)	0.92 (0.62–1.38)
≥25	31 (11.9)	24 (8.6)		0.63 (0.34–1.15)	0.46 (0.22–0.99)	0.90 (0.47–1.71)	0.83 (0.42–1.65)
Treatment history							
New case	86 (32.1)	158 (55.6)	<0.001	1	1	1	1
Previous 1st line	170 (63.4)	112 (39.4)		0.36 (0.25–0.51)	1.08 (0.65–1.79)	0.91 (0.64–1.30)	0.67 (0.42–1.06)
Previous 2nd line	12 (4.5)	14 (4.9)		0.64 (0.28–1.43)	1.74 (0.67–4.53)	2.09 (1.12–3.89)	1.65 (0.82–3.32)

Table 4 (*Continued*)

	Baseline characteristics			Predictors of care model		Predictors of attrition	
	Clinic, *n* (%)	Community, *n* (%)	*P*-value	OR (95% CI)	aOR (95% CI)	HR (95% CI)	aHR (95% CI)
TB site							
Pulmonary	257 (95.9)	275 (96.8)	0.557	1	1	1	1
Extrapulmonary	11 (4.1)	9 (3.2)		0.76 (0.31–1.88)	1.50 (0.52–4.33)	0.80 (0.30–2.17)	0.65 (0.23–1.81)
Smear status (n = 117, 21.2%)*							
Negative	52 (24.6)	51 (22.8)	0.134	1	1	1	1
Scanty/smear+	79 (37.4)	66 (29.5)		0.91 (0.56–1.50)	0.79 (0.43–1.45)	0.98 (0.57–1.71)	1.00 (0.56–1.79)
Smear++	30 (14.2)	33 (14.7)		1.12 (0.62–2.04)	1.44 (0.69–2.99)	1.03 (0.52–2.03)	1.12 (0.56–2.23)
Smear+++	50 (23.7)	74 (33.0)		1.38 (0.81–2.36)	1.60 (0.82–3.10)	1.22 (0.70–2.12)	1.33 (0.73–2.43)
DR-TB type							
RIF & INH resistance	104 (38.8)	91 (32.0)	0.004	1	1	1	1
RIF mono-resistance	62 (23.1)	104 (36.6)		1.92 (1.26–2.92)	1.23 (0.69–2.18)	0.81 (0.53–1.26)	0.96 (0.58–1.59)
INH mono-resistance	53 (19.8)	39 (13.7)		0.84 (0.51–1.39)	0.71 (0.38–1.34)	0.80 (0.46–1.38)	0.87 (0.49–1.54)
Empirical	49 (18.3)	50 (17.6)		1.17 (0.72–1.89)	1.80 (0.97–3.33)	1.55 (1.00–2.40)	1.66 (1.00–2.78)
HIV/ART/CD4 status (n = 14, 2.5%)*							
HIV-negative	47 (17.7)	59 (21.6)	0.527	1	1	1	1
HIV+ on ART, CD4 ≤ 200 cells/mm^3	95 (35.8)	80 (29.3)		0.69 (0.43–1.13)	0.75 (0.40–1.40)	1.10 (0.68–1.78)	1.08 (0.64–1.81)
HIV+ on ART, CD4 > 200 cells/mm^3	68 (25.7)	74 (27.1)		0.90 (0.55–1.49)	0.81 (0.42–1.54)	0.79 (0.47–1.35)	0.80 (0.45–1.42)
HIV+ without ART, CD4 ≤ 200 cells/mm^3	28 (10.6)	33 (12.1)		0.98 (0.52–1.85)	0.95 (0.43–2.12)	1.32 (0.73–2.38)	1.31 (0.69–2.49)
HIV+ without ART, CD4 > 200 cells/mm^3	27 (10.2)	27 (9.9)		0.82 (0.42–1.58)	0.84 (0.38–1.87)	0.86 (0.43–1.70)	0.79 (0.39–1.60)

We used multiple imputations in regression analyses for the variables BMI, smear status and HIV/ART/CD4 status. There was evidence of violation of the proportional hazard assumption for the variables age and care model. The flexible parametric survival model had three degrees of freedom (two internal knots) for non-time-dependent covariates and two degrees of freedom (one internal knot) for the time-dependent covariate age and care model. Analysis time starts at 14 days after DR-TB treatment initiation.

%, percentage; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; DR-TB, drug-resistant tuberculosis; HR, hazard ration; INH, isoniazid; INH+, isoniazid resistance; *n*, number; NPR, nurse-to-patient ratio; OR, odds ratio; RIF, rifampicin; RIF+, rifampicin resistance.

*Number and percentage of missing values.

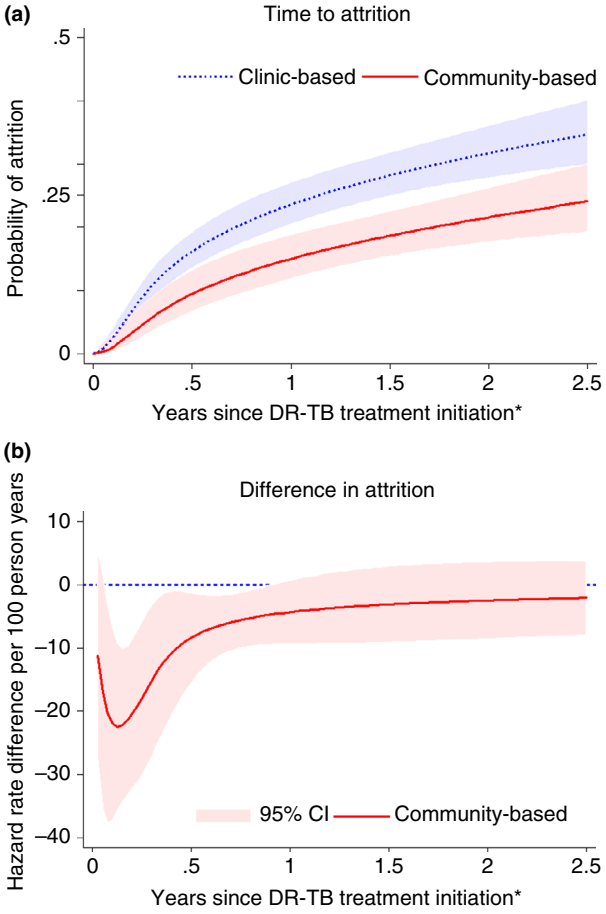


Figure 3 Attrition (a) and difference in hazard rates of attrition (b) for clinic-based and community-based care in Shiselweni (Eswatini), from January 2008 to December 2016. DR-TB, drug-resistant tuberculosis; CI, confidence interval. *Observation time starts at 2 weeks after DR-TB treatment initiation. [Colour figure can be viewed at wileyonlinelibrary.com].

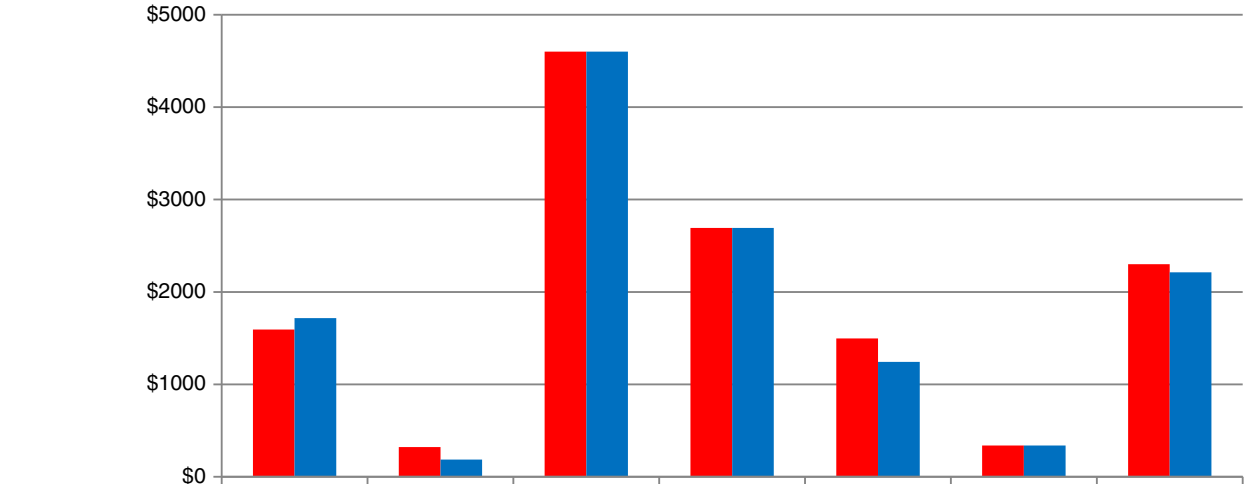
lacking. Secondly, an important programme component, as also recommended by WHO [18], was the patient-centred care approach (e.g. food provision) in both care models, which possibly facilitated treatment adherence in economically vulnerable patients. Thirdly, eliminating the requirement for daily travel to the facility for DOT probably reduced out-of-pocket expenses, making it easier for patients to complete therapy.

We identified changes in programme implementation over time, as well as opportunities for improvements. Firstly, in the early years and as per protocol, patients from more rural areas were more likely to be enrolled in community-based care. However, eligibility criteria widened in recent years, with 76.5% of patients being enrolled in community-based care in 2016, indicating increased acceptance of this care model by patients and health workers. In fact, geographical (rural setting) and temporal factors emerged as the main predictors of enrolment into community-based care. Secondly, efficiency was probably gained in community-based care during scale-up, with community DR-TB nurses following more patients (increased nurse-to-patient ratio). We believe that further programmatic efficiency gains can be achieved by keeping the nurse-to-patient ratio high and by full integration of HIV services.

Different DR-TB programmatic approaches have been implemented in RLS. Our DR-TB programme was informed by the local context and by programmes from Lesotho [4,13] and was guided by international recommendations [37]. Solely clinic-based care approaches [11,16,38] would probably have left behind patients from remote locations. Other community-based care models used nurses living near patients' homes or nurse-led mobile injection teams for daily home visits, DOT and treatment provision [12,39,40]. In our setting, patients received a monthly supply of oral and injectable drugs, and CTS ensured daily treatment provision, requiring fewer supervisory visits by health professionals. This less human resources intensive approach possibly safeguarded against treatment interruptions caused by health system failures.

Community-based care models may also reduce DR-TB transmission [41]. Hospitalisation is either not required or short, thus avoiding delays in treatment initiation and reducing the risk of nosocomial infections. In addition, infectious patients are not required to travel daily to the nearest treatment facility, possibly reducing the number of infectious contacts at community level.

Several obstacles to scalability of community-based care have been identified. Firstly, using CTS can be challenging in settings where law and traditions do not support their involvement in provision of care [18]. Attention is required to sufficient hands-on training, supervision by health professionals and support services in case of problems. In our setting, the community DR-TB nurse was always reachable by phone and could initiate support visits and patient transfer. Secondly, although community-based DR-TB care was perceived as expensive, programme costs were comparable between care models and the patient support package including monetary compensation for CTS accounted for 11% of the total costs of community-based care. These findings indicate the affordability of this community-based model from the health systems perspective. The costs of our care model were higher than in other RLS, but comparison is limited by differences in context and costing methodology [15].



	Personnel	Transport	Drugs	Laboratories	Incentives	HIV	Other
Total Community	$1593	$322	$4600	$2693	$1497	$338	$2301
Total Clinic	$1717	$187	$4600	$2693	$1242	$338	$2212

Figure 4 Total costs and cost categories of clinic-based and community-based care in Shiselweni (Eswatini), in 2012–2013. $, US dollar. The category 'Other' includes costs for the TB ward, infection control improvements at the patients' homes, support to deaf patients and training costs for community treatment supporters. [Colour figure can be viewed at wileyonlinelibrary.com].

Lastly, although it was beyond the scope of this analysis to assess temporal trends, we noticed an increase in DR-TB treatment cases during the first years followed by a decline thereafter. Several explanations exist. Firstly, the rapid decentralisation of HIV-TB services between 2008 and 2010 may have improved access to diagnosis and case detection of active TB for this predominantly rural population. Secondly, ART coverage increased rapidly in this high-HIV prevalence setting, from an estimated 7.1% in 2006 [42] to 82.7% in 2016/2017 [43]. In southern Africa, expansion of HIV treatment and high ART coverage are suggested key factors to decrease the burden of TB in people living with HIV and possibly also in the HIV-negative population [44]. In fact, TB notifications have decreased rapidly in Eswatini and the study area since 2009/2010 [45,46], despite increased case finding activities in more recent years, the introduction of the Xpert MTB/RIF assay, and strengthened infection control practice and TB care [47]. The decline in DR-TB is in line with the decline in all TB case notifications.

Perspectives

Community-based care should be considered when hospitalisation or clinic-based care models fail to provide universal access to uninterrupted DR-TB treatment. As shown in our setting, different care models can be complementary and implemented in the same setting. Governments, however, need to create an enabling environment, and task shifting and sharing can help to mobilise community assets for DR-TB care in RLS. Trained and supervised CTS could also be temporarily integrated into the health system, should receive sufficient supervision and support, and should be compensated for their work.

WHO recommends shorter (9–12 month) and prefers fully oral DR-TB treatment regimens [48]. Although newer drugs (e.g. bedaquiline) are also increasingly used in this setting [49], the need for innovative community-based solutions will persist as long as requirements for injectable drugs and DOT persist.

Limitations and strengths

Several limitations were identified. Firstly, non-random selection of patients with differences in baseline characteristics into care models may bias comparison. We attempted to control for this by identifying possible confounding factors *a priori* for inclusion into multivariate regression models and applied sensitivity analyses. For instance, although our analysis did not suggest that sicker patients were more likely to be selected for clinic-based care (e.g. based on baseline CD4 cell count and ART

status), we cannot rule out that health workers selected less sick patients for community-based care based on laboratory and clinical variables (e.g. biochemistry test results, clinical presentation) not available for this analysis and that other unmeasured factors of disease progression (e.g. WHO clinical staging) were comparable between groups. In addition, we may not have fully captured changes over time despite adjustment for temporal trends through the covariate programmatic period. The introduction of newer drugs (e.g. later generation fluoroquinolones, linezolid) and a more rapid diagnosis of DR-TB through the Xpert MTB/RIF assay may have resulted in better treatment outcomes in later years irrespective of care model. Yet, the later time-period coincided with higher enrolment into community-based care, thus possibly being a source of bias for the direct comparison of care models. Secondly, we included both DST-confirmed and empirical DR-TB treatment cases. To avoid treatment delays, clinicians were permitted to initiate and continue presumptive DR-TB treatment based on clinical suspicion. In RLS with high-HIV prevalence, TB diagnosis is difficult, missed or delayed in HIV co-infected patients, and culture-based tests are often reported late or are missing [50]. Thirdly, further studies are required to assess whether CTS support during the continuation phase would also be associated with improved outcomes. Lastly, although out-of-pocket expense may be a barrier to access and complete DR-TB treatment, we did not assess the patient's perspective due to lack of data.

A strength of this analysis is its large sample size compared with other similar studies. Secondly, sensitivity analyses using different model specifications and methodology supported the main findings. Thirdly, we included a broad range of DR-TB patients from a predominantly rural context, which is likely to be representative of many public sector settings in Africa.

Conclusions

Access to DR-TB treatment remains low in RLS. The use of trained treatment supporters in community-based DR-TB care may have overcome patient-level and programme-level barriers in this rural setting. Our data suggest that combining ambulatory care models and adapting them to the context can contribute to expansion of DR-TB treatment in RLS.

Acknowledgements

We acknowledge the extraordinary work of the community DR-TB team and community treatment supporters and their dedication to their patients without whom DR-TB care would have not been possible. We also acknowledge the support provided by the data collection team.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Programme characteristics of community-based and clinic-based care in Shiselweni (Eswatini), from January 2008 to December 2016.

Table S2. Outcome definitions.

Table S3. Sensitivity analyses of risk of attrition (SA-1 to SA-4) and risk of death (SA-5) for DR-TB treatment cases in Shiselweni (Eswatini), from January 2008 to December 2016.

Table S4. Total costs for DR-TB cases successfully treated over a 24-month period in community-based and clinic-based care in Shiselweni (Eswatini) in 2012–2013.

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