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Community- vs hospital-based management of multi-drug resistant tuberculosis in Pakistan: a randomised controlled trial

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Abstract

Background

Multi-drug resistant tuberculosis (MDR-TB) treatment takes 18-24 months and is complex, costly and isolating. We provide trial evidence on the WHO/Pakistan recommendation for community-based care rather than hospital-based care.

Methods

Two-arm, parallel-group, superiority trial was conducted in three programmatic management of drug-resistant tuberculosis hospitals in Punjab and Sindh provinces, Pakistan. We enrolled 425 MDR-TB patients >15 years through block randomization in Community-based care (one-week hospitalization) or Hospital-based care (two months hospitalization). Primary outcome was treatment success.

Results

Among 425 MDR-TB patients, 217 were allocated to Community-based care and 208 to Hospital-based care. Baseline characteristics were similar between the community and hospitalised arms as well as in selected sites. Treatment success was 74.2% (161/217) under Community-based care and 67.8% (141/208) under Hospital-based care, giving a covariate-adjusted risk difference (Community vs hospital model) of 0.06 (95% CI: -0.02, 0.15; P = 0.144).

Conclusions

We found no clear evidence that community-based care was more or less effective than hospital-based care model. Given the other substantial advantages of community-based care over hospital based (e.g., more patient friendly and accessible with lower treatment costs) this supports the adoption of Community based care model, as recommended by World Health Organization.

Trial registration: ISRCTN78224116.

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Background:

Multi-drug resistant tuberculosis (MDR-TB), defined as TB resistant to rifampicin and isoniazid, is a critical threat to global TB control, with nearly half a million cases of MDR-TB emerging every year. In 2020 Pakistan accounted for 5.8% of the world's TB cases and ranks 6th among countries that account for about 70% of the global gap between the estimated global incidence of MDR/RR-TB each year and the number of people enrolled in treatment in 2020. Given that the treatment success rate in 2018 for MDR-TB or rifampicin-resistant TB was 70% MDR-TB is clearly a very important health issue presenting great challenges for the public health sector in Pakistan and other high-burden TB/MDR-TB countries.

The management of MDR-TB is long (18-24 months) and complex requiring a system of continuing care with multiple technical and programmatic challenges [1]. An additional barrier is the policy, followed in Pakistan and many other countries, of hospitalising patients during the delivery of the intensive phase of treatment (usually lasting at least 6 months). However, shorter periods of hospitalisation increase hospital capacity to treat more patients, reduce infection risks and shorten the time to treatment initiation [2,3]. They also make treatment more accessible by making more of it available closer to the patient's home, thereby facilitating social and familial support for patients and their families [4–6]. An early start to community-based care could therefore help Pakistan and other resource-constrained programmes make more efficient use of limited resources to achieve WHO END-TB targets. For example, in South Asia the estimated average expected total treatment cost was US$ 3391 for the hospital-based model (HBC) and US$ 1724 for the decentralised model for a patient treated for MDR-TB [7]. While additional family costs, such as loss of earnings incurred during visiting, could also be avoided, and limiting patient visits to health facilities could reduce loss to follow-up and improve treatment outcomes.

Consequently, the World Health Organization (WHO) has recommended that community-based care for MDR-TB is adopted instead of hospital-based care, but this recommendation is based

on 'weak evidence' [8]. According to our systematic literature search (up to January 2021) the existing evidence is purely observational, and is summarised in two systematic reviews with meta-analyses of observational data comparing treatment effectiveness between community-based or hospital-based MDR-TB care [3,9], and a further systematic review comparing treatment effectiveness of home-based directly observed therapy (DOT) compared to hospital-based DOT [10] in MDR-TB treatment. All show that the community-based approach is either beneficial or not clearly different from the hospital-based approach.

At the time of implementing the trial (July 2013) usual care for MDR-TB patients in Pakistan was for patients to be treated in hospitals for the initial two months. However, to reduce financial and other barriers to families and providers, WHO Stop TB and Pakistan National TB Control Programme (NTP) were considering community based (also called ambulatory and decentralised) MDR-TB care. In 2013, NTP Pakistan and partners therefore conducted this randomised controlled trial (RCT) study to help inform the decision. Policy makers and clinicians in Pakistan and internationally recognise the cost and feasibility advantages of community-based care, but with a need to address concerns that treatment outcomes may not be as good as compared to hospital-based care. This RCT therefore aimed to evaluate the effectiveness of the community-based care model of MDR-TB treatment compared to the existing/usual care hospital-based treatment model, based on treatment success and other standard TB outcomes, to provide trial evidence about the WHO and NTP recommendation for community-based MDR-TB care.

METHODS

Trial reported following CONSORT guidelines.

Study design, setting and participants

This study used a two-arm, parallel-group, multicentre, superiority, individually RCT design to evaluate the effectiveness of the community-based model of MDR-TB compared to hospital-based care. When implemented there were 33 functional programmatic management of drug-resistant TB (PMDT) sites (28 public and 5 private) at the tertiary care level across Pakistan, and

three sites were selected for implementing the trial: Gulab Devi hospital, Ojha Institute and Samli Sanatorium Rawalpindi. The selection of trial sites was finalised after the assessment of potential sites and discussion with programme and hospital authorities, during the inception phase of the proposed trial. These sites were selected based on high numbers of MDR-TB patients, covering a large population and representing the two biggest provinces (Punjab & Sindh).

Eligible patients were those aged ≥15 years with a laboratory confirmed diagnosis of MDR-TB according national NTP guidelines, who were registered for treatment in a study PMDT site, and who were residents of a district with a strengthened directly observed therapy plus (DOTS-plus) clinic. Patients were excluded if they were suffering from severe conditions requiring hospitalization for oxygen inhalation, IV drugs, strict monitoring, if a family member was already recruited in the trial, if they had confirmed extreme drug resistance (XDR), or if they were pregnant.

Procedures

Patients in both arms received the same diagnostic services and treatment regimens as per the national guidelines[11] throughout their treatment, with the intensive phase of treatment being identical except for the following differences. In the hospital-based (usual) care arm patients were hospitalised initially for two months with hospital staff administering daily medication. After two months they were referred to a strengthened DOTS-plus clinic near their place of residence for community-based care. While in the community-based care arm patients were referred to a strengthened DOTS-plus clinic near to their place of residence for ambulatory care usually within seven days after their initial hospitalisation. The initial few days of hospitalisation were still necessary for baseline investigations, prescribing, education, initiating treatment and arranging a treatment supporter near the patient's home. After enrolment and following the initial evaluation patients were followed-up after 15 days for between 18-24 months until they had completed treatment or reached another outcome. See supplementary materials for further details.

Outcomes

Primary Outcome

The primary outcome was the patient-level binary outcome of treatment success (yes/no). Treatment success was defined as either being cured or completing treatment according to the programme protocol. More specifically, cured was defined as per WHO guidelines [12] as patients having at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture was reported during that time, and there was no concomitant clinical evidence of deterioration, a patient was also considered cured, provided that this positive culture was followed by a minimum of three consecutive negative cultures taken at least 30 days apart. Treatment completion was also defined as per WHO guidelines [12] as completion of the treatment course assuming sputum conversion to negative, but without a sputum result in the final months. Therefore, non-successful treatment was defined as being lost to follow-up, treatment failure, or death from any cause during the treatment period (again all defined according to WHO and NTP guidelines as described below).

Secondary Outcomes

All defined as per WHO guidelines [12]. 1. Cured (as defined above for part of the primary outcome but evaluated separately). 2. Treatment completion (as defined above, separately). 3. Lost to follow-up (also at 6 and 12 months): treatment interruption for two or more consecutive months for any reason without medical approval. 4. Treatment failure: treatment was considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy were positive, or if any one of the final three cultures is positive. Treatment was also considered to have failed if a clinician decided to terminate treatment early because of poor clinical or radiological response or adverse events. 5. Death: died for any reason during the course of treatment.

Sample size

Our sample size estimate indicated that we needed 428 patients in total. See the supplementary materials for full details.

Recruitment and randomisation

Trained medics and paramedic staff at the three selected MDR-TB sites identified and then recruited eligible MDR-TB cases, as per trial guidelines in consultation with an MDR-TB specialist. Patients who were not eligible followed routine care provided at the treating hospital. Once recruited the trial coordinator was informed via SMS and the NTP central research unit was called to get a randomisation code for the patient. The randomisation codes were produced prior to the trial by an independent statistician at the University of Leeds based random permuted blocks of size 4.

Statistical analysis

All analyses were conducted using Stata (version 14). In all inferential analyses we analysed all patients according to their original treatment allocation. As all outcomes were binary, we estimated both crude and covariate-adjusted treatment effects for all outcomes as both intervention-versus-control crude/covariate-adjusted risk differences and intervention-versus-control crude/covariate-adjusted risk ratios, using the Stata *adjrr* function (based on logistic regression models) [13]. We based our statistical inferences on the associated 95% confidence intervals and p-values (with the conventional level of statistical significance of $P \leq 0.05$). All covariate-adjusted results adjusted for study site (3 sites), patient age (≤30, 31-45, 46-60, >60) and patient sex (male/female).

Ethical considerations

Informed consent was obtained from each eligible patient prior to his/her recruitment. ISRCTN registry number: ISRCTN78224116. Ethical approval was obtained from the University of Leeds Research Ethics Committee (ref: HSLTLM11013) and at the national level from the ethical review committees of the Pakistan Medical and Research Council (ref: 4-87/12/NBC-102/RDC).

RESULTS

All patients were recruited between July 2013 and June 2016, and the follow-up and outcome measurements were completed by the end of May 2018. Figure 1 shows the trial flow diagram. Of the 425 MDR patients enrolled and randomised into the study 217 were allocated to the community-based care model and 208 were allocated to the hospital-based model. In the community-based care arm 17 (7.8%) patients were lost to follow-up and in the hospital-based care arm 28 (13.5%) patients were lost to follow-up. However, as lost to follow-up is a valid component of all our outcomes, we were able to collect all planned outcomes (and independent variable data) on all enrolled participants.

Baseline characteristics were broadly similar between the community and hospitalised treatment groups as well as in the selected PMDT sites (Table 1). There were more men as compared to women (55% male vs. 45% female) in the cohort overall. The age distribution was similar between community and hospitalised groups, with a majority (60%) of the patients being under 30 years of age. Patients in both arms were more likely to have a history of previously diagnosed TB (91.4% vs. 95.4%). However, patients randomised to the hospital-based care arm were less likely to have had a sputum smear positive at diagnosis (73.6% vs. 81.8%). At 6-months, the culture conversion rate was also slightly higher in community-based care arm (75.6% vs. 71%).

Across both arms, of the 425 patients initiated on MDR-TB treatment 302 (71.1%) had treatment success (the primary outcome), 58 (13.7%) died, 45 (10.6%) were lost to follow-up, 14 (3.3%) had treatment failure and 3 (0.7%) had treatment completion (Table 2). Within the community-based care arm 74.2% (161/217) of patients had treatment success and within the hospital-based care arm 67.8% (141/208) of patients had treatment success. The corresponding adjusted risk difference for treatment success (community-based care compared to hospital-based care) showed that although there was a small increase in the proportion of patients who had treatment success in the community-based care arm compared to the hospital-based care arm this was not statistically significant (adjusted risk difference = 0.064 [95%CI: -0.021, 0.148]; P = 0.144). Similarly, although all secondary outcome measures, including treatment failure,

loss to follow-up, and death, were slightly improved in the community-based care arm compared to the hospital-based care arm none of these differences were statistically significant (Table 2). None of the crude versions of the risk difference measures or the adjusted or crude risk ratio measures showed any substantive differences from these results (Tables 2 and 3). There was therefore no clear evidence of any beneficial nor any harmful treatment effect for the community-based care arm compared to the hospital-based care arm for any of the outcomes evaluated.

DISCUSSION

We found no statistically significant evidence of any beneficial or harmful treatment effect for the community-based care arm compared to the hospital-based care arm for any outcome. More specifically, the 95% confidence intervals for the adjusted risk difference estimate of treatment success implied that, within this study population, the actual risk difference is likely to be somewhere between a 2% reduction in treatment success and a 15% increase in treatment success for patients treated via the community-based care model compared to patients treated via the hospital-based care model. Clearly, a larger study is needed to confirm the precise nature of the effect of the community-based care model compared to the hospital-based care model in this population and setting with confidence.

The study has some additional limitations. We limited our analysis to the primary outcome of treatment success at the end of the treatment course, rather than post-treatment relapse, requiring follow-up beyond the 24 months, so we cannot provide an insight into the effects of the differing care models on such longer-term outcomes. We have also not assessed the costs of treatment in each care model, but this is unlikely to be higher for hospitalised care for either the patient and provider [7]. It was also not possible to blind patients or care providers to the treatment allocation of patients. However, we were able to follow-up all patients. Pakistan TB patients have low (0.66%) HIV co-positivity rate[14].Given the randomisation, we do not think patients co-morbidities including HIV will have influenced the outcome of the trial so we limited the analysis to outcomes of the trial only. The was also implemented under routine programme conditions, which increases the generalisability of the findings to similar non-trial settings, but

conversely it was only possible to conduct the trial in three, albeit large, purposively selected PMDT sites within the two big provinces of Pakistan, which clearly limits the generalisability.

At the time when the study was designed the hospital-based model of care was the standard of care in Pakistan, with concerns that decentralised community-based care would not achieve the same level of outcomes. However, community-based care has other benefits. These are primarily in terms of a more patient-friendly approach as patients are treated closer to home, allowing them easier and more convenient access to care, while minimising the requirement for long and frequent travel by family members to a centralised hospital, as well as, importantly, substantially lower costs of treatment [6,7,12,16]. But hospital-based model may be beneficial to educate patients on their condition, start & adherence of treatment, setup rehabilitation and nutrition plans, monitor adverse events, and reduce transmission in the community if patients are smear positive with the possibility to have reduced bacillary load before return to the community [6]. However, newer shorter MDR TB regimens may not require prolonged hospitalisation for two months[17].

To the best of our knowledge, this study is the only randomised controlled trial to date that has evaluated the effectiveness of a decentralised community-based care model for MDR-TB patients compared to a hospital-based model. Therefore, the results from this study may be cautiously taken as being supportive of the decision by the NTP to implement community-based MDR-TB care in Pakistan, despite not providing clear evidence of a benefit to the patient outcomes measured here. Internationally, these results also therefore provide randomised-trial-based evidence that supports the WHO's recommendation for community based MDR-TB care, which was previously based on observational study data alone [3,9,18].

Contributors

RF, AY, JW, AK and JPH did the literature review. AK, RF, EQ and JW designed the trial. The NTP Pakistan with AK and JW developed the case management guideline and training based on WHO MDR-TB guidance. RF, EQ, AG, MUH, NA, SB, AA, QA implemented the study. RF, AY, MUH prepared and cleaned the data. AY analysed the data. JPH provided substantial scientific input in statistical methods and interpretation of the results. RF, AY, JW and JPH prepared the

manuscript. All authors interpretation of data, revisions to the manuscript, and approved the final draft.

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Conflict of interests

Nothing to declare

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342 **Table 1. Baseline demographic and clinical characteristics of enrolled MDR-TB patients by treatment arm and by Programmatic**

343 **Management of Drug-resistant Tuberculosis site**

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Characteristics	Hospital-based model n (%)	Community-based model n (%)	Lahore site n (%)	Karachi site n (%)	Rawalpindi site n (%)
Sample size	208	217	208	176	41
Sex					
Male	115 (55.3)	120 (55.3)	91 (43.7)	79 (44.9)	20 (48.8)
Female	93 (44.7)	97 (44.7)	117 (56.3)	97 (55.1)	21 (51.2)
Age (years)					
≤30	117 (56.3)	125 (57.6)	123 (59.1)	94 (53.4)	25 (61.0)
31- 45	53 (25.5)	52 (24.0)	46 (22.1)	50 (28.4)	9 (22.0)
46 - 60	31 (14.9)	29 (13.4)	35 (16.8)	21 (11.9)	4 (9.8)
>60	7 (3.4)	11 (5.1)	4 (1.9)	11 (6.3)	3 (7.3)
History of previous TB	190 (91.4)	207 (95.4)	193 (92.8)	165 (93.8)	39 (95.1)

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Table 2. Covariate-adjusted treatment effect estimates for primary and secondary treatment outcomes of MDR-TB patients by treatment arm

Treatment outcomes	Total	Hospital-based model (N = 208) n (%)	Community-based model (N = 217) n (%)	Adjusted risk difference (95% CI); P-value	Adjusted risk ratio (95% CI); P-value
Primary Outcome					
Treatment success	302 (71.1)	141 (67.8)	161 (74.2)	0.064 (-0.021, 0.148); 0.144	1.09 (0.97, 1.23); 0.144
Secondary Outcomes					
Cured	299 (70.4)	139 (66.8)	160 (73.7)	0.070 (-0.016, 0.015); 0.113	1.10 (0.98, 1.25); 0.113
Treatment completed	3 (0.7)	2 (1.0)	1 (0.5)	-0.005 (-0.021, 0.011); 0.537	0.48 (0.04, 5.25); 0.537
Died	58 (13.7)	28 (13.5)	30 (13.8)	0.005 (-0.059, 0.070); 0.870	1.04 (0.65, 1.67); 0.870
Failed	14 (3.3)	8 (3.9)	6 (2.8)	-0.010 (-0.044, 0.024); 0.555	0.73 (0.26, 2.07); 0.555
Lost to follow-up	45 (10.6)	28 (13.5)	17 (7.8)	-0.059 (-0.113, 0.003); 0.07	0.58 (0.33, 1.03); 0.07
Not evaluated	6 (1.5)	3 (1.4)	3 (1.4)	-0.002 (-0.032,0.027) 0.886	0.89 (0.19, 4.29) 0.886

All results adjusted for the categorical variables: study site (3 sites), patient age (≤30, 31-45, 46-60, >60) and patient sex (male/female).

[a] Defined as cured or treatment completed.

354 **Table 3. Crude (covariate-unadjusted) treatment effect estimates for primary and secondary treatment outcomes of MDR-TB**
355 **patients by treatment arm**

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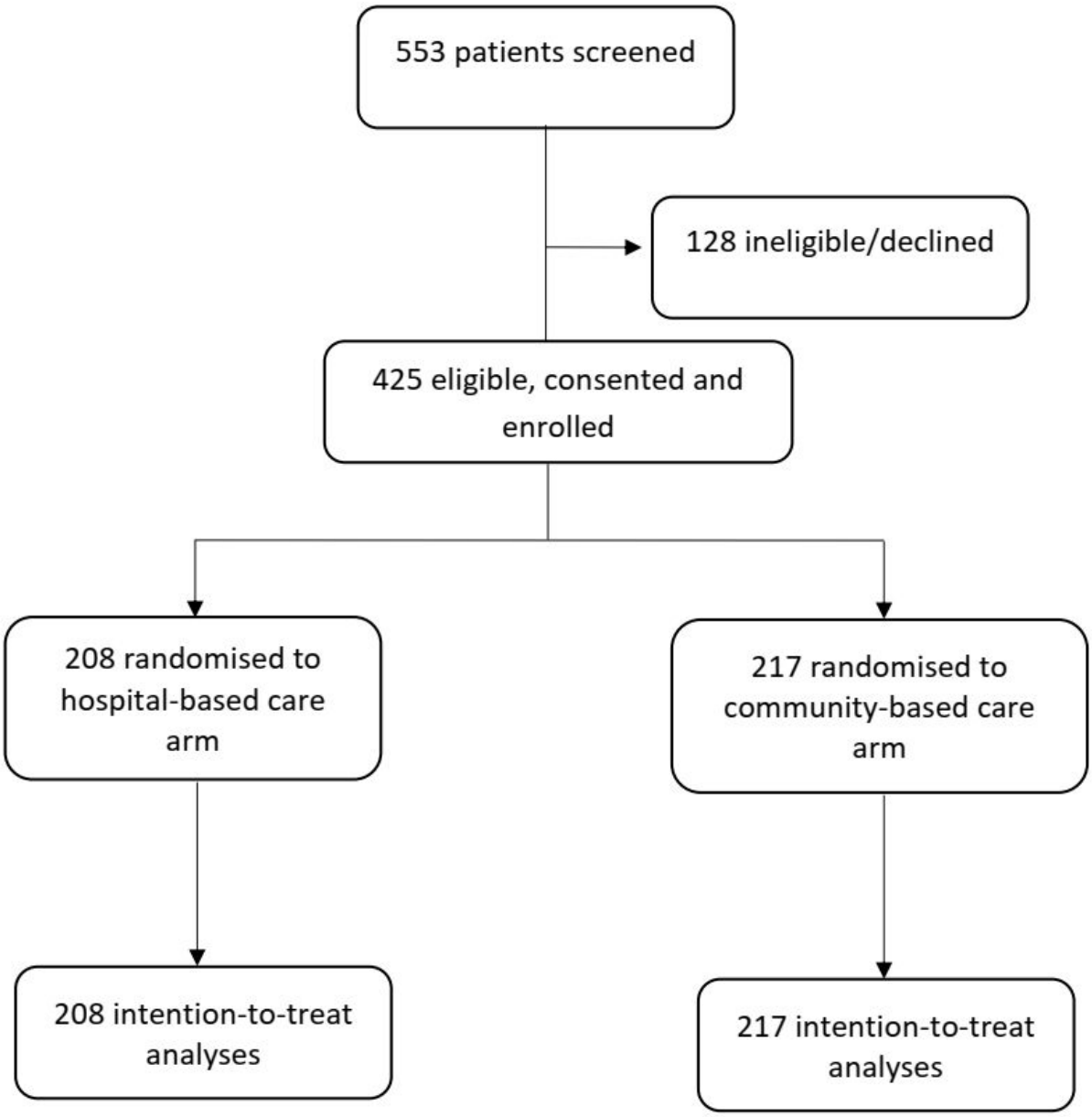
Treatment Outcomes	Total	Hospital-based model (N=208) n (%)	Community-based model (N=217) n (%)	Crude risk difference (95% CI); P-value	Crude risk ratio (95% CI); P-value
Primary Outcome					
Treatment success[a]	302 (71.1)	141 (67.8)	161 (74.2)	0.056 (-0.022,0.15); 0.145	1.09 (0.97,1.24); 0.145
Secondary Outcomes					
Cured	299 (70.4)	139 (66.8)	160 (73.7)	0.069 (-0.018, 0.156); 0.119	1.10 (0.97, 1.25); 0.119
Treatment completed	3 (0.7)	2 (1.0)	1 (0.5)	-0.005 (-0.021, 0.011), 0.538	0.45 (0.044, 5.24), 0.538
Died	58 (13.7)	28 (13.5)	30 (13.8)	0.004 (-0.062, 0.069); 0.913	1.03 (0.64, 1.66); 0.913
Failed	14 (3.3)	8 (3.9)	6 (2.8)	-0.011 (-0.045, 0.023); 0.532	0.72 (0.25, 2.04); 0.532
Lost to follow-up	45 (10.6)	28 (13.5)	17 (7.8)	-0.056 (-0.115, 0.002); 0.060	0.58 (0.33, 1.03); 0.060
Not evaluated	6 (1.5)	3 (1.4)	3 (1.4)	-0.001 (-0.023, 0.021); 0.958	1.00 (0.98, 1.02); 0.958

357 [a] Defined as cured or treatment completed.

358 **Figure 1. Trial flow diagram.**



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SUPPLEMENTARY MATERIALS

Additional methods details

Further site and setting details

In 2009 the Pakistan NTP, with the support of The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), developed the National Guidelines for programmatic management of drug-resistant TB (PMDT), and started piloting the management of drug resistant TB cases on hospital-based care. Currently, Pakistan has a well-established laboratory network including a National TB Reference Laboratory, 13 culture labs, 8 culture and drug-susceptible TB testing labs and 334 Xpert sites for diagnosis. There are currently 33 functional PMDT sites (28 public and 5 private) at the tertiary care level across Pakistan. They provide care which is free of cost including baseline and monitoring tests, as per NTP guidelines. Active pharmacovigilance measures are already in place at PMDT sites to ensure early detection and proper management of side effects. Health staff include a MDR-TB physician, PMDT pharmacist, MDR-TB PMDT site focal person, and the Head of Department of pulmonology is in charge of each PMDT site [1].

Further procedures details

The clinical and laboratory assessment, prescription, education, and treatment and social support components of care were the same for each registered MDR-TB patient. However, physical segregation of hospitalised patients was managed, to avoid contamination. The monthly follow-up assessment included clinical and laboratory assessment, as per programme guidelines. During the follow-up after two months of initial treatment, the staff responsible for clinical and laboratory assessment were kept blind (to the extent possible) to the duration of patient initial hospitalisation. After initial hospitalisation all trial patients visited the treating hospital on a monthly basis for follow-up assessment and supply of medication for a month, and so receive the same laboratory and clinical follow-up treatments. Patients with minor side effects were dealt with at the DOTS-plus clinic, and those with major side effects were immediately referred to the hospital. Patients were followed-up until they had completed treatment or reached another outcome (e.g. lost to follow-up), that is for between 18-24 months after enrolment following their initial evaluation. During the follow-up monthly clinical examination cultures and sputum samples were taken to monitor the response to treatment. The treatment protocols during the continuation phase were the same for both arms. In each hospital, the implementation of case management guidelines were monitored, as per programme guidelines, to standardise the practices. In addition, the research team at the national level monitored the activities to ensure adherence to trial protocols.

Further recruitment and randomisation details

The registration process for eligible patients was as follows. An information sheet was used to inform the eligible patient about the nature and purpose of the trial, the potential risks and benefits of participation in the trial and the hospitalisation required. The information sheet was handed over to those could read and asked to read it or read out loud, with any questions then answered. Consent was then taken where given using a consent form. Each eligible MDR-TB patient, after consenting to participate, was then registered into the trial.

The trail coordinator, on receiving a SMS/call regarding patient recruitment, made a record of the patient's details and provided allocation based on the randomisation code from the randomisation table. After receiving the allocation for the patient the patient was taken to the doctor to be admitted to the ward. If the patient opted out of the trial at this point then they continued the treatment of their choice, otherwise they continued with the allocated treatment protocol.

Further sample size details

The sample size was calculated using WHO sample size software (version 2). The level of significance (α) was 5%, power was 80%, the proportion of treatment success in the community-based care arm was assumed to be 55%, and the minimum risk ratio (improvement in the proportion of treatment success) desired to be detectable was assumed to be 1.35, and the sample size was inflated by 10%. Assuming an equal allocation ratio the estimate required at least 214 patients in each arm (a total of 428 patients). This sample size was also considered feasible in terms of available resources as well as recruitment of eligible patients.

Further statistical analysis details

Analyses were conducted using Stata version 14. Data quality assurance procedures were used that include training of data entry operators and checking data entry quality at regular intervals to minimise data errors. Baseline characteristics and treatment outcome were compared between hospital and community arms using descriptive statistics (means, standard deviations, frequencies and percentages) to assess whether randomisation resulted in equal distribution of characteristics.

In all inferential analyses we analysed according to the intention-to-treat principle, whereby we analysed all data according to the original allocation of individuals to treatment arms and using data from all individuals who were enrolled into the study, i.e. we only analysed the intention-to-treat population. As all outcomes were binary, we first calculated sample summary outcome measures for all outcomes as

frequencies and percentages by treatment arm. We then estimated covariate-adjusted treatment effects for all outcomes as both intervention-versus-control adjusted risk differences (i.e. between-arm difference in the proportion of individuals with the outcome of interest) and intervention-versus-control adjusted risk ratios (i.e. between-arm ratio in the proportion of individuals with the outcome of interest), along with their associated 95% confidence intervals and p-values to allow statistical inference. We calculated these adjusted treatment effect measures by fitting logistic regression models to the outcome data in Stata with a covariate for treatment arm and three additional categorical covariates considered important competing causal influences on the outcomes: study site (3 sites), patient age (≤30, 31-45, 46-60, >60) and patient sex (male/female). We again then used the *adjrr* function to calculate the adjusted risk differences and risk ratios [2]. We also calculated crude risk differences and risk ratios by following the same process but omitting all covariates from the logistic regression models other than treatment arm.

We treat the adjusted risk difference results as our primary results for determining the intervention's effectiveness, because by adjusting for important covariates these measures should provide less biased estimates of the treatment effects given any imbalances in characteristics between treatment arms, and by being on an absolute scale such measures provide a more useful measure of the likely public health impact of the intervention. We base our inferences about the effectiveness of the intervention on the p-values and 95% confidence intervals associated with these results, with the conventional level of statistical significance of 5% used as the basis for claiming evidence of intervention effectiveness.

Data management

Data was collected on routine recording and reporting forms in Electronic Nominal Recording Reporting System (ENRS) data which include sociodemographic, clinical, microbiological and treatment related data. Electronic data was stored and backed up monthly on a secured drive. Access to the raw datasets was granted to the data manager and trial coordinator and the hard copies are stored into a locked cabinet and were kept for at least 5 years.

REFERENCES

1. National TB Control Program. NTP Clinical Protocol For New Drugs (Bedaquiline & Delamanid) in Pakistan. Islamabad, Pakistan: Ministry of Health; 2016.
2. Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in Stata. Stata J. 2013;13: 492–509. doi:10.1177/1536867x1301300304