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Community vs hospital-based management of MDR-TB in Pakistan: a randomised controlled trial

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

3

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24

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34

For Review Only

35 Abstract**36 Background**

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

40 Methods

41 Two-arm, parallel-group, superiority trial was conducted in three programmatic management
42 of drug-resistant tuberculosis hospitals in Punjab and Sindh provinces, Pakistan. We enrolled
43 425 MDR-TB patients >15 years through block randomization in Community-based care (one-
44 week hospitalization) or Hospital-based care (two months hospitalization). Primary outcome
45 was treatment success.

46 Results

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

52 Conclusions

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

58 Trial registration: ISRCTN78224116.

59 Funding: UK Foreign, Commonwealth and Development Office via the COMDIS-HSD Research
60 Programme Consortium.

61 **Background:**

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

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

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

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

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

107 **METHODS**

108 Trial reported following CONSORT guidelines.

109 *Study design, setting and participants*

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

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

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

127 *Procedures*

128 Patients in both arms received the same diagnostic services and treatment regimens as per the
129 national guidelines¹¹ throughout their treatment, with the intensive phase of treatment being
130 identical except for the following differences. In the hospital-based (usual) care arm patients
131 were hospitalised initially for two months with hospital staff administering daily medication.
132 After two months they were referred to a strengthened DOTS-plus clinic near their place of
133 residence for community-based care. While in the community-based care arm patients were
134 referred to a strengthened DOTS-plus clinic near to their place of residence for ambulatory care
135 usually within seven days after their initial hospitalisation. The initial few days of hospitalisation
136 were still necessary for baseline investigations, prescribing, education, initiating treatment and
137 arranging a treatment supporter near the patient's home. After enrolment and following the
138 initial evaluation patients were followed-up after 15 days for between 18-24 months until they
139 had completed treatment or reached another outcome. See supplementary materials for further
140 details.

141

142 *Outcomes*

143 *Primary Outcome*

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

156 *Secondary Outcomes*

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

165 *Sample size*

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

168 *Recruitment and randomisation*

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

176 *Statistical analysis*

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

186 *Ethical considerations*

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

191

192 RESULTS

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

201 Baseline characteristics were broadly similar between the community and hospitalised
202 treatment groups as well as in the selected PMDT sites (Table 1). There were more men as
203 compared to women (55% male vs. 45% female) in the cohort overall. The age distribution was
204 similar between community and hospitalised groups, with a majority (60%) of the patients
205 being under 30 years of age. Patients in both arms were more likely to have a history of
206 previously diagnosed TB (91.4% vs. 95.4%). However, patients randomised to the hospital-
207 based care arm were less likely to have had a sputum smear positive at diagnosis (73.6% vs.
208 81.8%). At 6-months, the culture conversion rate was also slightly higher in community-based
209 care arm (75.6% vs. 71%).

210 Across both arms, of the 425 patients initiated on MDR-TB treatment 302 (71.1%) had
211 treatment success (the primary outcome), 58 (13.7%) died, 45 (10.6%) were lost to follow-up,
212 14 (3.3%) had treatment failure and 3 (0.7%) had treatment completion (Table 2). Within the
213 community-based care arm 74.2% (161/217) of patients had treatment success and within the
214 hospital-based care arm 67.8% (141/208) of patients had treatment success. The corresponding
215 adjusted risk difference for treatment success (community-based care compared to hospital-
216 based care) showed that although there was a small increase in the proportion of patients who
217 had treatment success in the community-based care arm compared to the hospital-based care
218 arm this was not statistically significant (adjusted risk difference = 0.064 [95%CI: -0.021, 0.148];
219 P = 0.144). Similarly, although all secondary outcome measures, including treatment failure,

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

227 **DISCUSSION**

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

237 The study has some additional limitations. We limited our analysis to the primary outcome of
238 treatment success at the end of the treatment course, rather than post-treatment relapse,
239 requiring follow-up beyond the 24 months, so we cannot provide an insight into the effects of
240 the differing care models on such longer-term outcomes. We have also not assessed the costs
241 of treatment in each care model, but this is unlikely to be higher for hospitalised care for either
242 the patient and provider ⁷. It was also not possible to blind patients or care providers to the
243 treatment allocation of patients. However, we were able to follow-up all patients. **Pakistan TB**
244 **patients have low (0.66%) HIV co-positivity rate¹⁴. Given the randomisation, we do not think**
245 **patients co-morbidities including HIV will have influenced the outcome of the trial so we limited**
246 **the analysis to outcomes of the trial only.** The was also implemented under routine programme
247 conditions, which increases the generalisability of the findings to similar non-trial settings, but

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

250 At the time when the study was designed the hospital-based model of care was the standard of
251 care in Pakistan, with concerns that decentralised community-based care would not achieve the
252 same level of outcomes. However, community-based care has other benefits. These are
253 primarily in terms of a more patient-friendly approach as patients are treated closer to home,
254 allowing them easier and more convenient access to care, while minimising the requirement for
255 long and frequent travel by family members to a centralised hospital, as well as, importantly,
256 substantially lower costs of treatment ^{6,7,12,16}. But hospital-based model may be beneficial to
257 educate patients on their condition, start & adherence of treatment, setup rehabilitation and
258 nutrition plans, monitor adverse events, and reduce transmission in the community if patients
259 are smear positive with the possibility to have reduced bacillary load before return to the
260 community ⁶. However, newer shorter MDR TB regimens may not require prolonged
261 hospitalisation for two months¹⁷.

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

270 *Contributors*

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

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

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289 *Conflict of interests*

290 Nothing to declare

291

292 **References**

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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**

344

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)

345

346

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

349

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

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

351 ^a Defined as cured or treatment completed.

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353

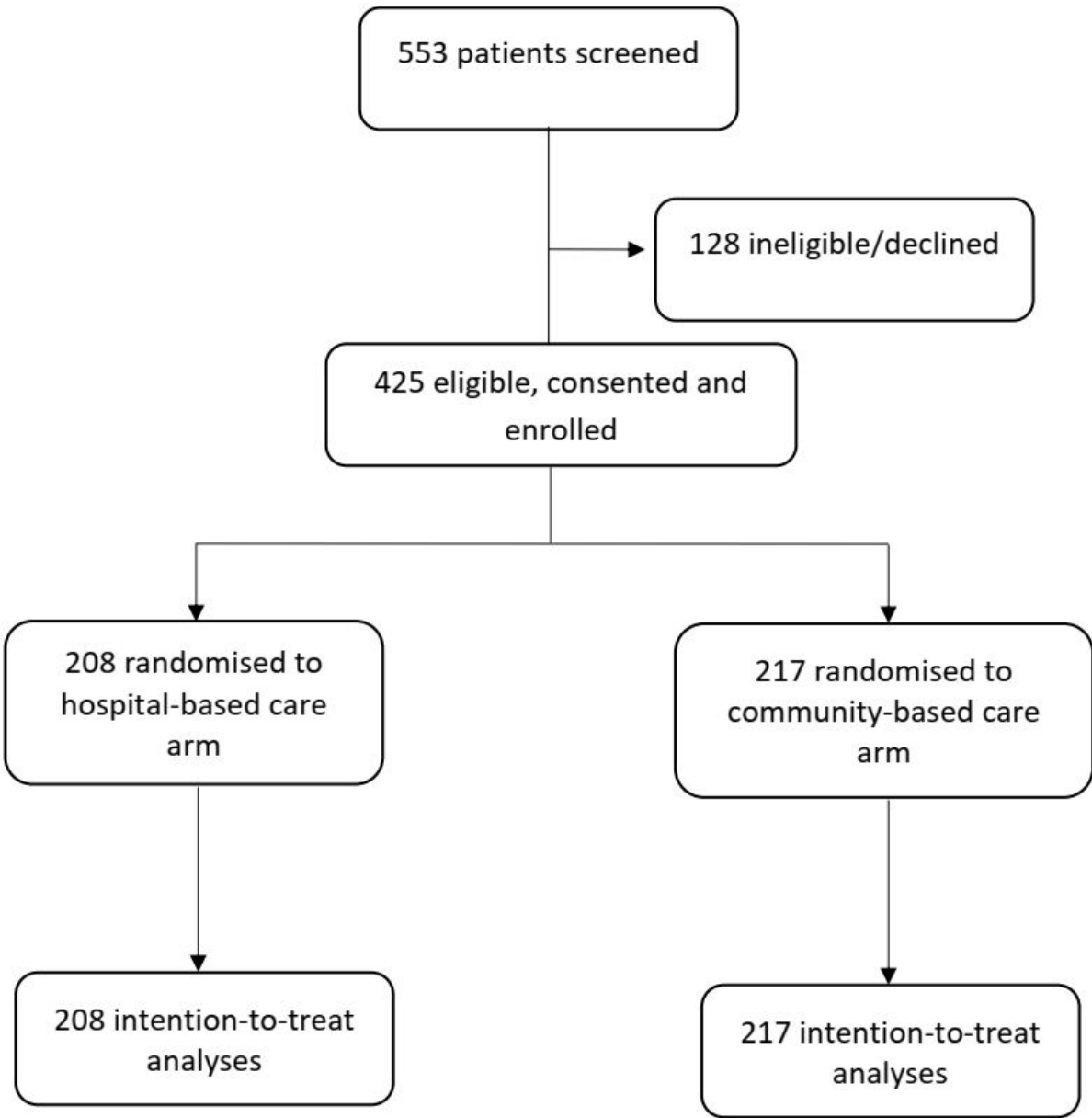
354 **Table 3. Crude (covariate-unadjusted) treatment effect estimates for primary and secondary treatment outcomes of MDR-TB**
 355 **patients by treatment arm**

356

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.**



359

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 trial 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.
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