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1 **Title: Temporal factors and missed doses of tuberculosis treatment: a causal**
2 **associations approach to analyses of digital adherence data**

3

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20

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35

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41 the project. All authors give final approval for the version to be published and agree to be
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43

44 **Data sharing statement:** The dataset supporting the conclusions of this article will be
45 available in the London School of Hygiene and Tropical Medicine Data Compass
46 (<http://datacompass.lshtm.ac.uk/>) repository. Potential users of these data should contact
47 KLF (katherine.fielding@lshtm.ac.uk) and acknowledge the data source in all subsequent
48 publications, presentations and reports.

49

50 **ABSTRACT**

51 **Rationale**

52 Tuberculosis treatment lasts for six months or more. Treatment adherence is critical;
53 regimen length, among other factors, makes this challenging. Globally, analyses mapping
54 common types of non-adherence are lacking. For example, is there a greater challenge from
55 early treatment cessation (discontinuation) or intermittent missed doses (suboptimal dosing
56 implementation)? This is essential knowledge for the development of effective interventions,
57 more 'forgiving' regimens, and to direct National Tuberculosis Programs.

58

59 **Objective**

60 Granularly describe how patients take their tuberculosis medication and the temporal factors
61 associated with missed doses.

62

63 **Methods**

64 Pulmonary tuberculosis patients enrolled in the control arm of a pragmatic cluster-
65 randomized trial in China of electronic reminders to improve treatment adherence were
66 included. Treatment was the standard six-month course (180 days), dosed every other day
67 (90 doses). Medication monitor boxes recorded adherence (box opening) without prompting
68 reminders.

69

70 Patterns of adherence were visualized and described. Mixed-effects logistic regression
71 models examined the temporal factors associated with per-dose suboptimal dosing
72 implementation, adjusting for clustering by participant. Cox regression models examined the
73 association between early suboptimal dosing implementation and permanent
74 discontinuation.

75

76 **Results**

77 Across 780 patients, 16,794 of 70,200 doses were missed (23.9%), 9,487 from suboptimal

78 dosing implementation (56.5%). By 60 days, 5.1% of participants had discontinued, 14.4%
79 by 120 days. Most participants (95.9%) missed at least one dose. The majority of gaps were
80 of a single dose (71.4%), although 22.6% of participants had at least one gap of two weeks'
81 or more.

82

83 In adjusted models, the initiation-continuation phase transition (odds ratio 3.07 [95%
84 confidence interval 2.68-3.51]) and national holidays (1.52 [1.39-1.65]) were associated with
85 increasing odds of suboptimal dosing implementation. Early-stage suboptimal dosing
86 implementation was associated with increased discontinuation rates.

87

88 **Conclusions**

89 Digital tools provide an unprecedented step-change in describing and addressing non-
90 adherence. In our setting, non-adherence was common; patients displayed a complex range
91 of patterns. Dividing non-adherence into suboptimal dosing implementation and
92 discontinuation, both were found to increase over time. Discontinuation was associated with
93 early suboptimal dosing implementation. These apparent causal associations between
94 temporal factors and non-adherence present opportunities for targeted interventions.

95

96 **Clinical trial registration**

97 ISRCTN46846388

98

99 **Primary source of funding**

100 Bill & Melinda Gates Foundation (51914)

101

102 **INTRODUCTION**

103 In 2017, 6.4 million incident tuberculosis (TB) cases were reported globally and an estimated
104 3.6 million went undiagnosed or were not notified.(1) Finding and treating these missing
105 patients is a key target of the World Health Organization (WHO); this requires substantial
106 international investment. It is critically important to protect this investment by providing
107 effective treatment to every diagnosed patient.

108

109 The standard treatment for drug sensitive TB lasts for six months. Numerous studies have
110 documented that patients struggle to adhere to the full course of therapy. An estimated 4-
111 35% demonstrate poor adherence.(2-11) Although various definitions have been used, poor
112 adherence is associated with a reduced likelihood of sputum conversion,(3) greater risk of
113 an unsuccessful treatment outcome,(4, 8, 12-15) and the development of drug
114 resistance.(16-19) Non-adherence to TB treatment is associated with various factors; those
115 that are patient-related, derived from the healthcare provider-patient relationship, the
116 regimen itself, and the healthcare system.(20)

117

118 In trials and observational studies, overly simplistic and non-evidence-based 80-90%
119 adherence thresholds have traditionally been used to signify adequate adherence.(12, 21-
120 23) Recently, however, the importance of highly accurate means of measuring adherence
121 within clinical trials has been acknowledged by WHO as a key part of trial design.(24)

122 Realistically, two core domains need to be considered when mapping adherence-
123 persistence (time between first and last doses; capturing initiation and discontinuation) and
124 dosing implementation (taking doses not as recommended e.g. skipping weekends).(25)

125 These components constitute 'therapeutic coverage', the proportion of time patients are
126 exposed to efficacious drug concentrations.(26) Detailed mapping of adherence patterns has
127 been missing from the TB literature to date.

128

129 Knowledge of how exactly TB patients take their medications and predictors of when non-

130 adherence is most likely to occur is critical for the directed design of interventions to improve
131 adherence, the development of regimens that are more ‘forgiving’ of non-adherence, and to
132 help clinicians know when to intervene with non-adherent patients. Currently, the relative
133 burden of suboptimal dosing implementation and discontinuation is unknown globally;
134 interventions to address these two components of non-adherence may look quite different.
135 This is a critical knowledge gap when it comes to reducing the burden of non-adherence,
136 which is impeding the most cost-effective implementation of the WHO guidelines on digital
137 adherence technologies for TB treatment.(27)

138

139 Utilizing data collected from a trial of electronic reminders to improve medication adherence
140 in China, we aimed to granularly describe how TB patients take their treatment and if
141 temporal factors were causally associated with missed doses in order to inform control
142 efforts. Components of this study have been previously reported through a conference
143 abstract.(28)

144

145

146 **METHODS**

147 **Parent study and study population for analysis**

148 The parent study- a pragmatic cluster randomized trial of electronic reminders to improve
149 treatment adherence among pulmonary TB patients in People’s Republic of China- from
150 which these data has been derived has been described before (Online supplement
151 Additional Methods).(29) Participants were enrolled into the study between 1st June 2011
152 and 7th March 2012. Only participants in the control arm of the trial were included in this
153 cohort study in order to capture usual patterns of treatment adherence in the absence of an
154 intervention (Online supplement Additional Methods).

155

156 **Measuring and defining adherence to treatment**

157 Adherence to each dose of treatment was documented by a medication monitor box (Online

158 supplement Additional Methods). The box captured every date and time on which it was
159 opened; box opening did not necessarily mean that drugs were taken. Medication was dosed
160 every other day (as per the National TB Program [NTP] standard at the time), for 90 doses
161 over a 180-day period. If the box was opened at least once within each two-day dosing
162 window this was recorded as adherence. The standard six-month regimen for drug sensitive
163 TB was used (two months of isoniazid, rifampicin, ethambutol, pyrazinamide, followed by
164 four months of isoniazid and rifampicin). Medication was not dosed in combination pills.

165

166 Non-adherence data from the monitor was coded, and categorized as a dose missed due to
167 suboptimal dosing implementation versus a dose missed due to permanent discontinuation,
168 using accepted terminology as per Vrijens *et al.*(25) Discontinuation was defined as ceasing
169 to adhere to treatment and not re-commencing both a) at any point during the 180-day
170 period and b) after this period but before the end of the trial. Discontinuation is different from
171 the programmatically defined term 'lost to follow-up' (previously known as 'default'), when
172 either a patient's treatment is interrupted for consecutive two months or more, or a patient
173 does not start treatment. Suboptimal dosing implementation refers to all doses missed
174 during the 180-day period, aside from those due to discontinuation. The term 'suboptimal' is
175 not intended to imply a judgement as to the appropriate level of adherence/type of
176 adherence pattern required to achieve a positive treatment outcome, but rather reflects an
177 implementation level below 100% of doses taken.

178

179 **Temporal exposures and potential confounders**

180 The following temporal measures were calculated from the medication monitor data: 1) day
181 of the week, 2) treatment month, 3) whether the dose fell on a Chinese national holiday, 4)
182 whether the patient was in the initiation or continuation phase of treatment (see Online
183 supplement Additional Methods).

184

185 Additionally, data were available for a series of potential confounders, all of which were self-

186 reported at entry into the study. These included age, sex, marital status, educational level,
187 occupation, household income, type of medical insurance, registration status, and distance
188 from home to TB clinic. The county/district in which the participant lived was grouped into
189 whether it was broadly rural or urban.

190

191 **Statistical methods**

192 ***Descriptive analyses***

193 Analyses were undertaken in Stata 15 and graphs plotted in Microsoft Excel.

194

195 Adherence to treatment was described using the following summary measures: the overall
196 percentage of doses taken, average duration that a patient was on treatment before ceasing
197 completely, percentage of participants achieving an 80% adherence threshold, and
198 percentage achieving a 90% threshold. In order to account for clustering, for each measure
199 the mean was calculated per county/district and then the geometric mean taken across the
200 county/district values.

201

202 Adherence over time, grouped by different percentage intervals, was graphically visualized
203 using lasagna plots, in which white indicates non-adherence.(30)

204

205 Line graphs were used to visualize non-adherence due to suboptimal dosing implementation
206 versus permanent discontinuation from treatment for all participants in the study and by
207 adherence levels in the initiation phase.(31) After plotting these graphs, we decided to
208 separate suboptimal dosing implementation and discontinuation in the remaining analyses.

209

210 The length and number of gaps in treatment due to suboptimal dosing implementation were
211 described using scatter plots.

212

213

214 ***Associations between temporal factors and suboptimal dosing implementation***

215 We used mixed-effects logistic regression to examine the factors associated with non-
216 adherence due to suboptimal dosing implementation, treating each dose as an observation
217 and adjusting for clustering by individual. We focused on temporal factors, including
218 weekends, national holidays, and the initiation-continuation phase transition (Model 1) or
219 treatment months (Model 2). Our methodology- including details of model selection through
220 the use of directed acyclical graphs, determination of *a priori* confounders, and assessment
221 of potential effect modification- is detailed elsewhere (Online supplement Additional
222 Methods). The impact of using different confounder sets on our findings was explored
223 through Models 1A-F (Online supplement Additional Methods). Both approaches sought to
224 address all confounding using different confounder sets to support the drawing of causal
225 conclusions from observational data.(32)

226

227 The potential presence of an interaction between the three temporal factors weekends,
228 national holidays, and the initiation-continuation phase transition and a) county/district or b)
229 distance from home to TB clinic were also explored using likelihood ratio tests (LRTs)
230 (Models 1G-H).

231

232 ***Associations between early suboptimal dosing implementation and time to***
233 ***discontinuation***

234 Cox proportional hazards regression was used to assess whether early suboptimal dosing
235 implementation, either in the initiation phase (Model 3) or month 1 (Model 4), was associated
236 with time to discontinuation. Individuals who had discontinued in the initiation phase and
237 month 1 were excluded, respectively, in order to preserve the temporality of the association.
238 Further details on adjustment for confounding, etc., are presented in Online supplement
239 Additional Methods. We report sensitivity analyses on the impact of confounding by
240 county/district (Models 3F, 4F) and excluding individuals who discontinued during the last
241 three doses of treatment (Models 3G, 4G). The potential presence of an interaction between

242 early suboptimal dosing and a) county/district or b) distance from home to the TB clinic were
243 also explored using LRTs.

244

245 **Ethical approval**

246 The trial was approved by the ethics committees of the Chinese Center for Disease Control
247 and Prevention (201008) and the London School of Hygiene & Tropical Medicine (5704). All
248 participants provided written consent prior to inclusion in the trial.

249

250

251 **RESULTS**

252 **Characteristics of the study population**

253 Of the 1,104 individuals randomized to the control arm of the trial, 209 (18.9%) had technical
254 issues with the medication monitor due to power outage problems, as indicated by the box
255 resetting the date to a baseline value (Online supplement Figure E1). A further 10.4% of
256 patients (115) were excluded, as events such as hospitalization for more than three days
257 removed the potential for treatment to be monitored for the entire period. Thus 780 (70.7%)
258 patient's data were available for analysis. A comparison of the included and excluded
259 patients revealed similarity in terms of baseline characteristics, except for county/district and
260 distance from home to the TB clinic (Table E1).

261

262 The baseline characteristics of participants are presented in Table 1. Individuals were
263 generally male (535, 68.6%). More than half were under the age of 50 (525, 67.3%).
264 Farming was the largest occupation (384, 49.2%), with 516 (66.2%) individuals living in
265 counties/districts deemed rural and 500 (64.1%) insured through rural co-operatives.

266

267 **Summary measures of overall adherence**

268 Across all 780 study participants, 70,200 doses were scheduled during the 180-day period;
269 16,794 of these were missed (23.9%). The geometric mean number of doses taken was

270 68/90 (75.6%). The geometric mean duration on treatment was 80 doses (i.e. 160 days)
271 before discontinuation.

272

273 **Overall adherence over time**

274 Lasagna plots of adherence over time demonstrated the distribution of participants in 20%
275 adherence intervals, with 473/780 (60.6%) in the highest category of ≥ 80 -100% adherent
276 (Figure 1). A clear 'staggered' pattern was observed in the lowest categories that
277 corresponded to drop-offs in adherence with each passing month (15 doses, 30 days).
278 Although there was a reduction in adherence over time, erratic non-adherence (suboptimal
279 dosing implementation) was observed throughout the treatment period.

280

281 The relative importance of non-adherence due to the permanent discontinuation of treatment
282 versus suboptimal dosing implementation is shown in Figure 2a. Of the 16,794 missed
283 doses, 9,487 were due to suboptimal dosing implementation (56.5%) and the remainder
284 discontinuation. The impact of discontinuation was demonstrably stronger over time. By the
285 end of month 2 5.1% of individuals had discontinued treatment; this figure was 14.4% by the
286 end of month 4 and continued to increase during the last two months, until it reached 36.3%
287 at the end of the 180-day period. The latter figure reflects the fact that discontinuation
288 captures treatment cessation without recommencement at any time point, including
289 cessation at the last (90th) dose.

290

291 When the 121 participants with <80% adherence in the initiation phase were examined
292 separately, they demonstrated sharp and sustained reductions in adherence due to both
293 discontinuation and suboptimal dosing implementation (Figure 2c).

294

295 **Gaps in adherence (suboptimal dosing implementation)**

296 Suboptimal dosing implementation was demonstrated by 748/780 (95.9%) participants i.e.
297 they displayed at least one gap in their treatment of one dose or more that was not due to

298 discontinuation. Overall, a total of 4,677 gaps were recorded, of which 71.4% (3,337/4,677)
299 were for one dose only. The population median of the median gap length per participant was
300 one and the interquartile range (IQR) 1-1 (Figure 3a). When the maximum gap length per
301 participant was examined, the median across the population was two doses (IQR 1-6; Figure
302 3b). Of the 780 individuals, 368 (47.2%) had at least one gap of three doses (roughly a
303 week) or more and 176 (22.6%) of seven doses (a fortnight) or more.

304

305 **Associations between suboptimal dosing implementation and temporal factors**

306 Our analysis of suboptimal dosing implementation and temporal factors was composed of
307 780 patients and 62,893 dose observations (Table 1). In unadjusted analyses, a strong
308 association was seen between the initiation-continuation phase transition and suboptimal
309 dosing implementation. The continuation phase was associated with triple the odds of
310 suboptimal dosing implementation (odds ratios [OR] 3.09 [95% confidence interval {CI} 2.70-
311 3.54]). This mirrors the month-by-month findings, where suboptimal dosing implementation
312 increased from 6.8% of doses in treatment month 1 to 19.7% in month 6. Sunday was
313 associated with greater suboptimal dosing implementation than the other days of the week
314 ($p < 0.001$). Compared to weekdays, weekends were associated with a small increase in the
315 odds of suboptimal dosing implementation (1.13 [1.07-1.19]). National holidays were
316 associated with a larger increase in odds (1.62 [1.49-1.75]; 14.6% to 20.5%).

317

318 In an adjusted model controlling for age as a linear variable, sex and urban/rural setting, and
319 with a random effect on the initiation-continuation variable ([LRT p-value < 0.001), all three
320 temporal variables were associated with greater odds of suboptimal dosing implementation
321 (weekends: 1.14 [1.08-1.20]), national holiday: 1.52 [1.39-1.65]), initiation-continuation
322 transition 3.07 [2.68-3.51] (Model 1). There was no evidence for interactions between the
323 initiation-continuation transition and national holidays (LRT p-value 0.97) or weekends (LRT
324 p-value 0.07). These findings were robust to adjustment for different combinations of
325 confounders (Table E2; Models 1A-F).

326

327 Tests for interaction were performed between the three temporal factors and county/district
328 or distance. For distance, the LRT p-values for the initiation-continuation phase transition,
329 holidays and weekends were 0.52, 0.97 and 0.91, respectively. For county/district, the LRT
330 p-values for the initiation-continuation phase transition, holidays and weekends were 0.01,
331 <0.001, 0.79, respectively. We thus undertook stratified analyses by county/district of the
332 relationship between suboptimal implementation and a) the initiation-continuation phase
333 transition (Table E3, Model 1G) or b) holidays (Table E4, Model 1H). Although the
334 magnitude of the relationship between these two temporal factors and suboptimal
335 implementation altered by county, the direction of effect was the same in all instances,
336 barring one instance where the CI crossed the null (Baiquan, Model 1H; 0.94 [0.75-1.18]).

337

338 Given the striking initiation-continuation phase effect found in these models, but also the
339 more gradual pattern of reducing adherence demonstrated in Figure 1, the association
340 between treatment month and suboptimal dosing implementation was assessed. A random
341 effect was included on the treatment month (LRT p-value <0.001), which was treated as a
342 categorical variable. An interaction was documented between treatment month and national
343 holidays (LRT p-value 0.01), but the statistical evidence was less certain for an interaction
344 between treatment month and weekends (LRT p-value 0.06).

345

346 Within a model containing the treatment month-national holiday interaction (Model 2), the
347 association between weekends and the odds of non-adherence due to suboptimal dosing
348 implementation changed little from Model 1 (1.14 [1.08-1.20]). From month-to-month, the
349 likelihood of suboptimal dosing implementation approximately increased and was particularly
350 pronounced for doses that fell on national holidays (Table 2). A dose falling on a national
351 holiday was positively associated with suboptimal dosing implementation, with the largest
352 increase in odds in the last month of treatment, but no clear trend month-to-month (Table 2).

353

354 **Associations between time to discontinuation and early suboptimal dosing**
355 **implementation**

356 Among the individuals included in the study, 109 were found to stop treatment without
357 recommencing within the 90-dose period, but to later recommence before the end of the trial.
358 The latest dose taken was at 254 days. These individuals were not classified as
359 discontinuing. Patients who discontinued during the relevant implementation period were
360 excluded in order to preserve temporality within any associations. Thus, 740 patients
361 contributed to an analysis of discontinuation and suboptimal dosing implementation in the
362 initiation phase and 775 when suboptimal dosing implementation in month 1 was instead
363 considered (Table 1).

364

365 In unadjusted analyses, increased suboptimal dosing implementation in the initiation phase
366 and month 1 were associated within an increase in the likelihood of discontinuation (Table
367 1). These findings were robust in an adjusted analysis (Table 3). The impact of ≥ 80 to $< 90\%$
368 versus $\geq 90\%$ adherence was less certain for the initiation phase analysis (Model 3), but
369 more suggestive of a dose-response association in the month 1 analysis (Model 4).
370 Considering different confounder sets, these models were robust to adjustment for a fixed
371 effect for county/district rather than urban/rural (Table E5; Models 3F and 4F). When the 52
372 individuals who discontinued from dose 87 onwards were excluded, our effect estimates
373 increased for both the initiation phase and month 1 analyses (Table E5; Models 3G and 4G).
374 Tests for interaction between early suboptimal dosing implementation and county/district
375 revealed no evidence for an effect (LRT p-value 0.19).

376

377 **DISCUSSION**

378 Our analysis of adherence- both suboptimal dosing implementation and discontinuation-
379 among pulmonary TB patients in China provides the first detailed description of how doses
380 are missed over the six-month treatment period. We found that participants took 76% of their
381 doses; 61% took 80% or more. The use of simple percentage thresholds, however, masks

382 important variation in the patterns of missed doses over time.

383

384 Of all missed doses, 43% were due to discontinuation. A steady increase in non-adherence
385 due to both suboptimal dosing implementation and discontinuation over time was observed.

386 At two months, 5.1% of participants had discontinued their medication, 14.4% at four
387 months, and 36.3% by the end of the 180-day period. During the intensive phase of
388 treatment (the first two months), suboptimal dosing implementation accounted for the
389 majority of non-adherence. Of the 19% of patients who were non-adherent at the end of the
390 intensive phase, discontinuation accounted for 27% of the non-adherence and suboptimal
391 dosing implementation the remainder. During the continuation phase (months 3 to 6), the
392 odds of suboptimal dosing implementation were three times higher than during the intensive
393 phase, but the percentage of patients with suboptimal dosing implementation remained
394 stable at 17-20%. However, the percentage of those who discontinued treatment continued
395 to accumulate, and by the fifth month, discontinuation accounted for 52% of all non-
396 adherence.

397

398 We identified an important association between suboptimal dosing implementation early in
399 the course of treatment and subsequent discontinuation. Suboptimal dosing implementation
400 in the first month or overall initiation phase (months 1 and 2) was associated with higher
401 discontinuation rates. Across participants, 96% demonstrated suboptimal dosing
402 implementation; around three quarters of gaps were for one dose only. Nevertheless, 47% of
403 individuals had potentially clinically important gaps of three consecutive doses or more and
404 23% of seven consecutive doses (a fortnight) or more. The odds of suboptimal dosing
405 implementation were higher on national holidays (OR 1.52).

406

407 The findings of this study provide several insights into how drug-sensitive TB treatment can
408 be improved. Firstly, NTPs should take seriously the problem of non-adherence to treatment,
409 which is under-recognized. In this study, a high percentage of patients had gaps of a week

410 or more in their treatment due to suboptimal dosing implementation. If these gaps are not
411 recognized and treatment is not adjusted accordingly, then long-term, relapse-free, cure of
412 these patients may be compromised. NTPs should place a much higher priority on improving
413 adherence during treatment and not simply focus on ensuring completion.

414

415 Second, this study identified the importance of early adherence. Adherence worsened over
416 the course of treatment, especially after the shift into the continuation phase. We also found
417 an association between discontinuation and early suboptimal dosing implementation. Thus
418 improving adherence early in the course of treatment may be important to prevent later non-
419 adherence.

420

421 Third, this study highlights the importance of granular adherence data on individual patients.
422 Early identification of individuals with poor adherence or who discontinue would improve the
423 likelihood of success of adherence-promoting interventions. Identification of such individuals
424 could result in the initiation of differentiated care, which would include more tailored
425 adherence support for these patients. The design of such behavioral interventions should
426 take into account data on the types of non-adherence displayed by the target population and
427 their causes. For example, plans to support medication adherence may need to be
428 proactively generated with patients before holiday periods, where travel to different locations
429 may generate greater concern about stigma and result in missed doses. Adherence should
430 also be monitored after such interventions are deployed, to check for improvement. Digital
431 technologies to record adherence- e.g. by using pill bottle opening as a surrogate for
432 medication intake- have been available for many years and are starting to be rolled out
433 globally, despite operational barriers such as cost.(33) Such technologies, however, provide
434 an opportunity to monitor TB treatment adherence for individual patients on a large
435 scale.(33)

436

437 Fourth, these results lend support to the development of shorter treatment regimens, which

438 may avoid the adherence drop-off later in treatment that is currently observed. Such
439 regimens have not yet demonstrated non-inferiority (34-36) and will likely, however, increase
440 the importance of each individual dose in ensuring cure. Retrieving patients who default from
441 treatment is a large financial burden on NTPs; this could also be reduced with shorter
442 regimens that result in less discontinuation. We also highlight the value of examining
443 discontinuation of treatment, rather than programmatically defined loss to follow-up/default,
444 in terms of capturing effective drug exposure.

445

446 Overall, studies prior to ours have provided the initial basis of a link between different
447 adherence patterns and treatment outcomes in drug sensitive disease.(2-9, 11) For
448 example, missing 8-16% of doses has been associated with 25 times the odds of remaining
449 sputum positive,(3) adhering below a 90% threshold with 5.9 times the rate of an
450 unfavorable outcome,(15) adhering below a 75% threshold with 3.2 times the odds of
451 recurrence,(14) adhering below a 90% threshold with 3.4 times the odds of mortality,(4) and
452 'irregular' drug taking such that treatment had to be extended 2.5 times increased odds of
453 relapse.(8) Conversely, a regimen simulating <67% adherence had no impact on
454 recurrence.(37) Additionally, previous studies have documented a 17% additional hazard per
455 month of acquired drug resistance if adherence is <80%,(19) or 19.7 times the odds of with
456 half month gaps, non-engagement or <80% adherence.(16) This association is not simple;
457 particularly poor adherence may exert little selective pressure.(17) In drug resistant disease,
458 there is a smaller but less contradictory evidence base in terms of the implications of non-
459 adherence: long interruptions and <80-90% adherence have been associated with poorer
460 outcomes.(17, 19, 38, 39) What these studies lack- which potentially explains their
461 conflicting findings- is a granular exploration of how non-adherence influences treatment
462 outcomes using reliable sources of adherence data.(23) Our study indicates that poor
463 adherence is complicated and heterogeneous; future studies will require granular dose-by-
464 dose data in order to properly assess the non-adherence-outcomes relationship. Future
465 studies should collect detailed adherence data- moving away from monthly self-reported

466 information and chart reviews- to ascertain how they correlate to therapeutic coverage,
467 pharmacokinetics (TB drugs with a short half-life are predicted to be less forgiving), sputum
468 conversion rates, treatment outcomes,(40) relapse (the gold standard outcome measure),
469 and the development of drug resistance.

470

471 This is the most detailed analysis to date of treatment adherence in TB, which makes use of
472 exceptionally granular adherence data. It does, however, have its limitations. Whether drug
473 intake was supported (e.g. observed by a family member) or self-administered was not
474 documented, potentially leaving residual confounding. Opening the medication monitor box
475 does not necessarily mean that drugs were taken, although a validation study has indicated
476 high correlation with urine rifampicin levels.(41) Given that each dose could have been taken
477 during a two-day period, non-differential misclassification of the temporal exposure variables
478 may have occurred, biasing effect estimates towards the null. As fixed dose combination pills
479 were not used, it is possible that non-adherence was underestimated per drug, as individuals
480 may have chosen not to take all their pills per dose. The exclusion of participants for whom a
481 whole dosing history was not available may have resulted in selection bias, as excluded
482 participants differed from included participants in terms of the county/district in which they
483 lived and their distance from home to their local TB clinic. On the basis of tests for
484 interaction, it seems unlikely, however, than temporal factors (the focus of our analysis) are
485 systematically differently associated with adherence across different levels of these
486 variables. Data were missing on participant's personal holidays, which could be biasing the
487 effect size towards the null. Furthermore, part of the national holiday effect could represent
488 individuals not transporting their monitor boxes with them when they travel, but nevertheless
489 taking their medication. Socio-behavioral data on factors associated with non-adherence,
490 such as stigma, were not collected, potentially resulting in residual confounding. Finally,
491 participants may have been aware that they would be less likely to have taken their drugs at
492 weekends and thus switched their doses from weekends to weekdays to avoid non-
493 adherence. This is a function of the every-other-day dosing of the regimen and would result

494 an over-emphasized effect size.

495

496 Four key factors in our study affect generalizability: this was a 1) single country dataset of 2)

497 pulmonary TB patients 3) enrolled in a trial who 4) took their drugs every other day. Being

498 enrolled in a trial is thought to boost adherence and the individuals who consent to

499 participate are often more likely to be adherent; adherence data are therefore also needed

500 from observational studies globally.(42-44) We thus recommend the need for future studies

501 using granular adherence data from observational studies undertaken in other nations.

502

503 **CONCLUSIONS**

504 In conclusion, we demonstrate how non-adherence to TB treatment is a complex issue that

505 needs to be taken seriously. Adherence worsens over the course of treatment, but early-

506 stage interventions (when suboptimal dosing implementation is first detected) may prevent

507 later discontinuation. For such interventions to be accurately targeted to the patients most in

508 need, individual-level adherence data is required on a large scale. Shorter TB treatment

509 regimens may reduce the impact of worsening adherence over the treatment course.

510

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512 Not applicable.

513

514 **VISUAL ABSTRACT**

515 A visual abstract is included with this manuscript.

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645

646 **FIGURE LEGENDS**

647 **Figure 1. Lasagna plot of adherence**

648 Each patient of the 780 participants in the control arm of the original trial is a row in the
649 graph; white indicates a dose that has not been taken. Adherence calculated as a
650 percentage of the 90 doses taken over the 180-day period and then grouped into 20%
651 adherence intervals. Rows are colored by adherence group. Numbers in brackets indicate
652 the number of individuals within each 20% adherence interval.

653

654 **Figure 2. Relative contribution of discontinuation and suboptimal dosing
655 implementation to non-adherence over time**

656 Non-adherence due to discontinuation (ceasing treatment and not re-commencing; dark
657 grey) versus suboptimal dosing implementation (sporadic missed doses; light grey) over time
658 in a) the 780 control arm patients from the original trial, b) the 659 patients would displayed
659 $\geq 80\%$ adherence during the initiation phase, c) the 121 patients who displayed $< 80\%$
660 adherence in the initiation phase. Discontinuation is ceasing treatment at any stage,
661 including only for the 90th dose. If, after the 90th dose, another was taken before the end of
662 the trial, the patient is not recorded as having discontinued. Discontinuation is not the same
663 as programmatically defined loss to follow-up/default. Graph style adapted from the work of
664 Blaschke *et al.*[28]

665

666 **Figure 3. Gaps in adherence**

667 Gaps during the 90-dose medication period among the 748 participants who displayed
668 suboptimal dosing implementation. Number of gaps per participant of any length plotted
669 against a) the median gap length per participant, b) the maximum gap length per participant.

670

671
672

Table 1. Baseline characteristics. Unadjusted analyses of factors associated with non-adherence due to suboptimal dosing implementation or discontinuation

| Exposure variables | Overall | | Analysis of suboptimal dosing implementation | | | | | Analysis of discontinuation | | |
|--|--------------|--------------|--|--------------|--------------|-------------|------------------------|-----------------------------|-------------------------------|------------------------|
| | Participants | Col. % | Doses | Col. % | Doses missed | Row % | Unadjusted OR (95% CI) | Person time (doses) | Participants who discontinued | Unadjusted HR (95% CI) |
| Overall | 780 | 100.0 | 62893 | 100.0 | 9487 | 15.1 | - | 62396 | 235 | - |
| Sex | | | | | | | | | | |
| Female | 245 | 31.4 | 19804 | 31.5 | 2683 | 13.5 | baseline | 19649 | 161 | baseline |
| Male | 535 | 68.6 | 43089 | 68.5 | 6804 | 15.8 | 1.20 (0.99-1.45) | 42747 | 74 | 1.00 (0.76-1.32) |
| Age categorized (years) | | | | | | | | | | |
| <30 | 230 | 29.5 | 18305 | 29.1 | 2837 | 15.5 | baseline | 18157 | 69 | baseline |
| 30-39 | 128 | 16.4 | 10099 | 16.1 | 1315 | 13.0 | 1.01 (0.95-1.08) | 10021 | 44 | 0.95 (0.87-1.04) |
| 40-49 | 167 | 21.4 | 13518 | 21.5 | 2077 | 15.4 | | 13422 | 56 | |
| 50-59 | 136 | 17.4 | 11117 | 17.7 | 1712 | 15.4 | | 11023 | 35 | |
| 60+ | 119 | 15.3 | 9854 | 15.7 | 1546 | 15.7 | | 9773 | 31 | |
| Occupation | | | | | | | | | | |
| Students | 32 | 4.1 | 2529 | 4.0 | 428 | 16.9 | 1.01 (0.64-1.58) | 2512 | 13 | 1.34 (0.76-2.37) |
| Worker | 74 | 9.5 | 6102 | 9.7 | 722 | 11.8 | 0.61 (0.45-0.84) | 6048 | 17 | 0.69 (0.42-1.15) |
| Migrant Worker | 74 | 9.5 | 6167 | 9.8 | 815 | 13.2 | 0.76 (0.55-1.03) | 6115 | 17 | 0.68 (0.41-1.13) |
| Farmer | 384 | 49.2 | 30763 | 48.9 | 5347 | 17.4 | baseline | 30523 | 122 | baseline |
| Unemployed/ Houseworker | 63 | 8.1 | 5207 | 8.3 | 624 | 12.0 | 0.60 (0.43-0.84) | 5165 | 17 | 0.81 (0.49-1.35) |
| Other | 153 | 19.6 | 12125 | 19.3 | 1551 | 12.8 | 0.68 (0.53-0.86) | 12033 | 49 | 1.02 (0.73-1.42) |
| Educational level | | | | | | | | | | |
| Illiterate | 60 | 7.7 | 4595 | 7.3 | 858 | 18.7 | 1.38 (0.92-2.07) | 4557 | 20 | 1.43 (0.79-2.59) |
| Lower middle school | 494 | 63.3 | 39999 | 63.6 | 6254 | 15.6 | 1.03 (0.78-1.35) | 39692 | 154 | 1.25 (0.82-1.93) |
| Upper middle school | 130 | 16.7 | 10571 | 16.8 | 1216 | 11.5 | 0.73 (0.52-1.02) | 10484 | 37 | 1.13 (0.68-1.89) |
| University or more | 96 | 12.3 | 7728 | 12.3 | 1159 | 15.0 | baseline | 7663 | 24 | baseline |
| Total household income in last calendar year (RMB) | | | | | | | | | | |
| ≥20,000 | 446 | 57.2 | 36044 | 57.3 | 4994 | 13.9 | baseline | 35754 | 131 | baseline |
| <20,000 | 334 | 42.8 | 26849 | 42.7 | 4493 | 16.7 | 1.31 (1.10-1.57) | 26642 | 104 | 1.07 (0.83-1.38) |
| Medical insurance | | | | | | | | | | |
| Rural co-op | 500 | 64.1 | 40583 | 64.5 | 6604 | 16.3 | 1.23 (0.96-1.57) | 40261 | 146 | 0.65 (0.48-0.89) |
| Urban workers | 92 | 11.8 | 7843 | 12.5 | 946 | 12.1 | 0.86 (0.61-1.20) | 7773 | 18 | 0.40 (0.24-0.69) |
| No insurance | 132 | 16.9 | 9855 | 15.7 | 1350 | 13.7 | baseline | 9786 | 53 | baseline |
| Other | 56 | 7.2 | 4612 | 7.3 | 587 | 12.7 | 0.95 (0.64-1.41) | 4576 | 18 | 0.71 (0.42-1.21) |
| Marital status | | | | | | | | | | |
| 1st marriage | 551 | 70.6 | 45024 | 71.6 | 6707 | 14.9 | baseline | 44665 | 161 | baseline |
| Unmarried | 184 | 23.6 | 14421 | 22.9 | 2194 | 15.2 | 1.02 (0.82-1.26) | 14305 | 57 | 1.11 (0.82-1.50) |
| Other | 45 | 5.8 | 3448 | 5.5 | 586 | 17.0 | 1.15 (0.78-1.69) | 3426 | 17 | 1.43 (0.87-2.35) |

Table 1. continued

| Exposure variables | Overall | | Analysis of suboptimal dosing implementation | | | | | Analysis of discontinuation | | |
|---|--------------|--------|--|--------|--------------|-------|------------------------|-----------------------------|-------------------------------|------------------------|
| | Participants | Col. % | Doses | Col. % | Doses missed | Row % | Unadjusted OR (95% CI) | Person time (doses) | Participants who discontinued | Unadjusted HR (95% CI) |
| County | | | | | | | | | | |
| Baiquan | 100 | 12.8 | 7629 | 12.1 | 1926 | 25.2 | baseline | 7581 | 46 | baseline |
| Yilan | 103 | 13.2 | 8683 | 13.8 | 1113 | 12.8 | 0.40 (0.29-0.56) | 8605 | 15 | 0.26 (0.15-0.47) |
| Rugao | 78 | 10.0 | 6366 | 10.1 | 844 | 13.3 | 0.39 (0.27-0.56) | 6310 | 21 | 0.52 (0.31-0.87) |
| Jianhu | 80 | 10.3 | 6938 | 11.0 | 1270 | 18.3 | 0.60 (0.42-0.86) | 6878 | 13 | 0.29 (0.16-0.54) |
| Miluo | 85 | 10.9 | 6961 | 11.1 | 1131 | 16.2 | 0.55 (0.39-0.78) | 6905 | 24 | 0.55 (0.34-0.90) |
| Yueyanglou | 81 | 10.4 | 5893 | 9.4 | 718 | 12.2 | 0.35 (0.24-0.50) | 5856 | 42 | 1.21 (0.79-1.83) |
| Fengjie | 70 | 9.0 | 5115 | 8.1 | 684 | 13.4 | 0.39 (0.27-0.56) | 5088 | 40 | 1.34 (0.88-2.04) |
| Shapingba | 79 | 10.1 | 6311 | 10.0 | 915 | 14.5 | 0.49 (0.34-0.70) | 6258 | 18 | 0.45 (0.26-0.78) |
| Jiangbei | 104 | 13.3 | 8997 | 14.3 | 886 | 9.8 | 0.29 (0.21-0.40) | 8915 | 16 | 0.27 (0.16-0.49) |
| Rural/urban | | | | | | | | | | |
| Rural | 516 | 66.2 | 41692 | 66.3 | 6968 | 16.7 | baseline | 41367 | 159 | baseline |
| Urban | 264 | 33.8 | 21201 | 33.7 | 2519 | 11.9 | 0.67 (0.55-0.81) | 21029 | 76 | 0.94 (0.71-1.23) |
| Residence | | | | | | | | | | |
| Living in place of household registration | 658 | 84.4 | 53187 | 84.6 | 8191 | 15.4 | baseline | 52768 | 198 | baseline |
| Not living in place of household registration | 122 | 15.6 | 9706 | 15.4 | 1296 | 13.4 | 0.80 (0.62-1.03) | 9628 | 37 | 1.03 (0.72-1.46) |
| Distance from home to local TB clinic (km) | | | | | | | | | | |
| <10 | 188 | 24.1 | 15984 | 25.4 | 2255 | 14.1 | baseline | 15847 | 37 | baseline |
| 10-19 | 191 | 24.5 | 15185 | 24.1 | 2199 | 14.5 | 1.05 (0.99-1.12) | 15065 | 63 | 1.14 (1.04-1.24) |
| 20-29 | 118 | 15.1 | 9596 | 15.3 | 1451 | 15.1 | | 9524 | 40 | - |
| 30-39 | 149 | 19.1 | 11802 | 18.8 | 1782 | 15.1 | | 11714 | 49 | - |
| >=40 | 134 | 17.2 | 10326 | 16.4 | 1800 | 17.4 | | 10246 | 46 | - |
| Day | | | | | | | p<0.001 | | | |
| Sunday | - | - | 9009 | 14.3 | 1516 | 16.8 | baseline | - | - | - |
| Monday | - | - | 8997 | 14.3 | 1301 | 14.5 | 0.81 (0.74-0.89) | - | - | - |
| Tuesday | - | - | 8939 | 14.2 | 1344 | 15.0 | 0.84 (0.77-0.92) | - | - | - |
| Wednesday | - | - | 9004 | 14.3 | 1315 | 14.6 | 0.83 (0.76-0.91) | - | - | - |
| Thursday | - | - | 8895 | 14.1 | 1426 | 16.0 | 0.93 (0.85-1.01) | - | - | - |
| Friday | - | - | 9275 | 14.7 | 1251 | 13.5 | 0.74 (0.68-0.81) | - | - | - |
| Saturday | - | - | 8774 | 14.0 | 1334 | 15.2 | 0.87 (0.80-0.95) | - | - | - |

Table 1. continued

| Exposure variables | Overall | | Analysis of suboptimal dosing implementation | | | | | Analysis of discontinuation | | |
|-----------------------------|--------------|--------|--|--------|--------------|-------|------------------------|-----------------------------|-------------------------------|------------------------|
| | Participants | Col. % | Doses | Col. % | Doses missed | Row % | Unadjusted OR (95% CI) | Person time (doses) | Participants who discontinued | Unadjusted HR (95% CI) |
| Weekend | - | - | | | | | p<0.001 baseline | - | - | - |
| Weekday | - | - | 45110 | 71.7 | 6637 | 14.7 | | - | - | - |
| Weekend | - | - | 17783 | 28.3 | 2850 | 16.0 | 1.13 (1.07-1.19) | - | - | - |
| Month | - | - | | | | | p<0.001 baseline | - | - | - |
| 1 | - | - | 11687 | 18.6 | 789 | 6.8 | | - | - | - |
| 2 | - | - | 11298 | 18.0 | 1383 | 12.2 | 2.92 (2.60-3.28) | - | - | - |
| 3 | - | - | 10800 | 17.2 | 1857 | 17.2 | 5.35 (4.66-6.13) | - | - | - |
| 4 | - | - | 10314 | 16.4 | 1843 | 17.9 | 5.78 (4.91-6.81) | - | - | - |
| 5 | - | - | 9770 | 15.5 | 1839 | 18.8 | 6.31 (5.21-7.65) | - | - | - |
| 6 | - | - | 9024 | 14.3 | 1776 | 19.7 | 6.26 (5.01-7.83) | - | - | - |
| National holidays | - | - | | | | | p<0.001 baseline | - | - | - |
| No | - | - | 58018 | 92.2 | 8487 | 14.6 | | - | - | - |
| Yes | - | - | 4875 | 7.8 | 1000 | 20.5 | 1.62 (1.49-1.75) | - | - | - |
| Phase | - | - | | | | | p<0.001 baseline | - | - | - |
| Initiation | - | - | 22985 | 36.5 | 2172 | 9.4 | | - | - | - |
| Continuation | - | - | 39908 | 63.5 | 7315 | 18.3 | 3.09 (2.70-3.54) | - | - | - |
| Initiation phase adherence* | - | - | | | | | | | | p=0.003 baseline |
| ≥90% | - | - | - | - | - | - | - | 47419 | 137 | |
| 80-90% | - | - | - | - | - | - | - | 7373 | 22 | 1.05 (0.67-1.64) |
| <80% | - | - | - | - | - | - | - | 6819 | 36 | 1.98 (1.37-2.86) |
| Month 1 adherence** | - | - | | | | | | | | p=0.003 baseline |
| ≥90% | - | - | - | - | - | - | - | 51106 | 171 | |
| 80-90% | - | - | - | - | - | - | - | 7471 | 34 | 1.39 (0.96-2.00) |
| <80% | - | - | - | - | - | - | - | 3757 | 25 | 2.10 (1.38-3.19) |

676 Leftmost data columns: baseline characteristics of the 780 individuals from the control arm of the original trial. Middle data columns: unadjusted mixed-effects
677 logistic regression for the 780 individuals included in the analysis of suboptimal dosing implementation. Each model adjusted for clustering by patient. Age
678 and distance to TB clinic modelled as linear variables. Random effect modelled on the initiation-continuation phase and month variables within the relevant
679 unadjusted model. Rightmost data columns: unadjusted Cox regression for the 780 individuals included in the analysis of discontinuation. *740 individuals in
680 the initiation phase adherence model and **775 in the month 1 adherence model; these exposure variables document non-adherence due to suboptimal
681 dosing implementation only. Age and distance to TB clinic modelled as linear variables. All columns: no data were missing for any of the variables. - - not
682 applicable, CI- confidence interval, Col- column, HR- hazard ratio, km- kilometres, OR-odds ratio, RMB- Renminbi, TB- tuberculosis

683 **Table 2. Adjusted odds ratios for the association between suboptimal dosing**
684 **implementation and a) treatment month, stratified by national holidays or b) national**
685 **holidays, stratified by treatment month**

| | | National holidays | |
|---|---|--------------------------|--------------------|
| | | No | Yes |
| Treatment month, stratified by national holidays | | | |
| Treatment month | 1 | baseline | baseline |
| | 2 | 2.87 (2.55-3.23) | 3.32 (2.15-5.15) |
| | 3 | 5.23 (4.55-6.01) | 5.82 (3.81-8.90) |
| | 4 | 5.58 (4.72-6.58) | 7.34 (4.76-11.31) |
| | 5 | 6.23 (5.13-7.57) | 6.45 (4.11-10.12) |
| | 6 | 5.90 (4.71-7.40) | 10.01 (6.27-15.98) |
| National holidays, stratified by treatment month | | | |
| Treatment month | 1 | baseline | 1.25 (0.85-1.84) |
| | 2 | baseline | 1.45 (1.15-1.82) |
| | 3 | baseline | 1.39 (1.16-1.67) |
| | 4 | baseline | 1.64 (1.36-1.98) |
| | 5 | baseline | 1.29 (1.06-1.58) |
| | 6 | baseline | 2.12 (1.71-2.62) |

686 Adjusted regression of the association between non-adherence due to suboptimal dosing
687 implementation and treatment month, stratified by national holidays (top rows) or national holidays,
688 stratified by treatment month (bottom rows); Model 2. 62,893 doses from 780 individuals from the
689 control arm of the original trial included. The stratum-specific ORs are adjusted for weekends, age,
690 sex and rural-urban. Random effect modelled on the month variable. Age modelled as a linear
691 variable. Results per cell presented as OR (95% CI). CI- confidence interval, OR- odds ratio
692

693 **Table 3. Adjusted Cox regression models of the association between early suboptimal**
 694 **dosing implementation and discontinuation**

| Temporal factor | Hazard ratio (95% CI) |
|----------------------------|-----------------------|
| MODEL 3 | |
| Initiation phase adherence | p=0.004 |
| ≥90% | baseline |
| 80-<90% | 1.04 (0.66-1.63) |
| <80% | 1.97 (1.36-2.85) |
| MODEL 4 | |
| Month 1 adherence | p=0.004 |
| ≥90% | baseline |
| 80-<90% | 1.37 (0.95-1.99) |
| <80% | 2.06 (1.35-3.15) |

695 Model 3 examines the association between non-adherence in the initiation phase due to suboptimal
 696 dosing implementation and discontinuation, adjusting for age, sex and rural-urban. It excludes
 697 individuals who discontinued in the initiation phase, leaving 740. Model 4 examines the association
 698 between non-adherence in the month 1 due to suboptimal dosing implementation and discontinuation,
 699 adjusting for age, sex and rural-urban. It excludes individuals who discontinued during month 1,
 700 leaving 775. Age modelled as a linear variable. CI- confidence interval
 701

1 **ONLINE SUPPLEMENT**

2

3 **Temporal factors and missed doses of tuberculosis treatment: a causal associations**

4 **approach to analyses of digital adherence data**

5

6 Helen R. Stagg, James J. Lewis, Xiaoqiu Liu, Shitong Huan, Shiwen Jiang, Daniel P. Chin,

7 Katherine L. Fielding

8

9 **Additional Methods**

10 ***Parent study and study population for analysis: additional details***

11 Between 1st June 2011 and 7th March 2012, in the Heilongjiang, Jiangsu, Hunan, and
12 Chongqing provinces of the People's Republic of China, 4,173 eligible pulmonary TB
13 patients placed on the standard six-month anti-tuberculosis regimen were consented to be
14 enrolled in a pragmatic cluster randomized trial of electronic reminders (short message
15 service [SMS] and audio reminders from a medication monitor box) to improve treatment
16 adherence.(1) The thirty-six clusters were rural counties or urban districts within these
17 provinces. In all arms of the study, each month a patient's medication was placed in their
18 medication monitor box by local health service staff. The box captured every date and time
19 on which it was opened. These data were downloaded at the monthly clinic visits, at which
20 new medication was dispensed.

21
22 Within the control arm of the trial, participants were managed according to the standard of
23 care of the National TB Control Program (NTP). They received no electronic reminders to
24 take their medications; their treatment was either self-administered, or supervised by family
25 members or health care workers. Further restrictions to be included within the cohort
26 analyzed in this study were: having no power outage problems with the medication monitor
27 (resulting in box opening not being recorded), no hospital inpatient stay greater than three
28 days, no pausing/stoppage of treatment due to side effects, and being enrolled into the trial
29 on the same day as TB registration such that treatment had not already started and thus all
30 doses could be captured.

31
32 ***Measuring and defining adherence to treatment: interpreting data from the medication***
33 ***monitor***

34 Data from the medication monitor box were interpreted as follows. If the box was opened at
35 least once within each two-day dosing window this was recorded as adherence, together
36 with the date. If the box was not opened within this period no adherence data were recorded

37 by the monitor. To document non-adherence at any point, we inferred the dates of missed
38 doses and thus non-adherence when the monitor did not record being opened. Data from
39 the first 180 days were used in the analysis; data on doses taken after this period were not
40 used.

41

42 ***Temporal exposures and confounding: additional information about categorization***

43 The following temporal measures were calculated from the medication monitor data: 1) the
44 day of the week on which each expected dose of medication fell, 2) the treatment month of
45 the dose (expected doses 1-15 fell in month 1, etc.), 3) whether the expected dose fell on a
46 Chinese national holiday, and finally 4) the first 30 expected doses were assigned to the
47 initiation phase of treatment and the last 60 doses to the continuation phase. The latter
48 division is the norm for TB treatment; in the initiation phase four drugs are used for two
49 months, in the continuation phase two drugs are used for four months. The Chinese national
50 holidays considered were New Year (January), Chinese New Year (January), Tomb
51 Sweeping Day (April), Labor Day (April/May), The Dragon Boat festival (June), mid-autumn
52 festival (September), and National Day (October).

53

54 Levels of suboptimal dosing implementation in the initiation phase and month 1 were also
55 calculated and categorized.

56

57 ***Associations between temporal factors and suboptimal dosing implementation:***

58 ***detailed methodology used***

59 Adherence data were included for each patient up until the last dose taken before a
60 permanent stoppage of treatment (discontinuation) or the 180-day end point of the regimen,
61 whichever was sooner. Doses after the 180-day (90 dose) point were considered when
62 assessing discontinuation, however (see Methods: Measuring and defining adherence to
63 treatment).

64

65 Our analyses focused on the temporal factors of weekends, national holidays and,
66 separately, either the initiation-continuation phase transition (Model 1) or treatment months
67 (Model 2). Having drawn a directed acyclical graph (DAG), the following were deemed a
68 *priori* confounders: age, sex and rural-urban. Assessing the effect of treatment months in
69 place of the initiation-continuation phase transition was decided upon *ad hoc*, after
70 examining our line graphs.

71

72 When building our main adjusted model (Model 1) the following factors were additionally
73 considered from the DAG. On the basis of biological plausibility age, treatment month and
74 distance to tuberculosis (TB) clinic were selected *a priori* for an assessment of goodness of
75 fit as linear or categorical variables. Effect estimates across strata were compared and
76 likelihood ratio tests (LRTs) undertaken. Additionally, interactions between national
77 holidays/weekends and the initiation-continuation phase transition or treatment month were
78 tested for using LRTs. The impact of adding a random effect for treatment month and
79 initiation-continuation phase, such that their effect varied between individuals, was also
80 assessed using LRTs.

81

82 Model 1 was adapted by adjusting for different sets of potential confounders in place of rural-
83 urban in addition to the *a priori* confounders. These potential confounders could not all be
84 simultaneously assessed due to collinearity. The confounder sets were: distance from home
85 to local TB clinic (Model 1A), medical insurance (Model 1B), occupation (Model 1C), rural-
86 urban and education level (Model 1D), rural-urban and total household income in the last
87 year (Model 1E).

88

89 A sensitivity analysis was conducted to examine the impact of potential clustering by
90 county/district, by including this variable as a fixed effect in place of rural-urban (Model 1F).
91 It could not be included as a random effect, due to the small number of counties/districts.

92

93 ***Associations between early suboptimal dosing implementation and time to***

94 ***discontinuation: detailed methodology used***

95 Non-adherence due to suboptimal dosing implementation was categorized into three levels:
96 <80%, 80-89% and ≥90%. The same *a priori* confounders and rural-urban variable were
97 adjusted for as previously, on the basis of a DAG. The validity of the proportional hazards
98 assumption was assessed using a likelihood ratio test (LRT) for an interaction between time
99 and the main exposure of interest.

100

101 A sensitivity analysis was also conducted for Models 3 and 4 using a fixed effect for
102 county/district in place of rural-urban status (Models 3F and 4F). An additional analysis
103 excluded individuals who discontinued during the last three doses (approximately a week), in
104 order to focus on earlier time points of discontinuation (Models 3G and 4G).

105

106 **Table E1. Comparison of baseline characteristics between individuals included in and**
 107 **excluded from the analysis cohort**

108 p-values from X² tests.

| Exposure variables | Analysis dataset | | | | p-value |
|--|------------------|-------------|------------|-------------|---------|
| | Included | Col. % | Excluded | Col. % | |
| Overall | 780 | 70.7 | 324 | 29.3 | |
| Sex | | | | | p=0.09 |
| Male | 535 | 68.6 | 239 | 73.8 | |
| Female | 245 | 31.4 | 85 | 26.2 | |
| Age categorised (years) | | | | | p=0.73 |
| <30 | 230 | 29.5 | 103 | 31.8 | |
| 30-39 | 128 | 16.4 | 49 | 15.1 | |
| 40-59 | 303 | 38.8 | 129 | 39.8 | |
| 60+ | 119 | 15.3 | 43 | 13.3 | |
| Occupation | | | | | p=0.28 |
| Students | 32 | 4.1 | 22 | 6.8 | |
| Worker | 74 | 9.5 | 27 | 8.3 | |
| Migrant Worker | 74 | 9.5 | 24 | 7.4 | |
| Farmer | 384 | 49.2 | 156 | 48.1 | |
| Unemployed/Houseworker | 63 | 8.1 | 22 | 6.8 | |
| Other | 153 | 19.6 | 73 | 22.5 | |
| Educational level | | | | | p=0.61 |
| Illiterate | 60 | 7.7 | 21 | 6.5 | |
| Lower middle school | 494 | 63.3 | 199 | 61.4 | |
| Upper middle school | 130 | 16.7 | 64 | 19.8 | |
| University or more | 96 | 12.3 | 40 | 12.3 | |
| Total household income in last calendar year (RMB) | | | | | p=0.92 |
| ≥20,000 | 320 | 41.0 | 134 | 41.4 | |
| <20,000 | 460 | 59.0 | 190 | 58.6 | |
| Medical insurance | | | | | p=0.56 |
| Rural co-op | 500 | 64.1 | 210 | 64.8 | |
| Urban workers | 92 | 11.8 | 42 | 13.0 | |
| No insurance | 132 | 16.9 | 56 | 17.3 | |
| Other | 56 | 7.2 | 16 | 4.9 | |
| Marital status | | | | | p=0.41 |
| 1st marriage | 551 | 70.6 | 219 | 67.6 | |
| Unmarried | 184 | 23.6 | 80 | 24.7 | |
| Other | 45 | 5.8 | 25 | 7.7 | |
| County | | | | | p<0.001 |
| Baiquan | 100 | 12.8 | 25 | 7.7 | |
| Yilan | 103 | 13.2 | 20 | 6.2 | |
| Rugao | 78 | 10.0 | 40 | 12.3 | |
| Jianhu | 80 | 10.3 | 39 | 12.0 | |
| Miluo | 85 | 10.9 | 33 | 10.2 | |
| Yueyanglou | 81 | 10.4 | 38 | 11.7 | |
| Fengjie | 70 | 9.0 | 60 | 18.5 | |
| Shapingba | 79 | 10.1 | 52 | 16.0 | |
| Jiangbei | 104 | 13.3 | 17 | 5.2 | |
| Rural/urban | | | | | p=0.79 |
| Rural | 516 | 66.2 | 217 | 67.0 | |
| Urban | 264 | 33.8 | 107 | 33.0 | |

109

110 **Table E1. continued**

| Exposure variables | Analysis dataset | | | | p-value |
|---|-------------------------|---------------|-----------------|---------------|----------------|
| | Included | Col. % | Excluded | Col. % | |
| Residence | | | | | p=0.97 |
| Living in place of household registration | 658 | 84.4 | 273 | 84.3 | |
| Not living in place of household registration | 122 | 15.6 | 51 | 15.7 | |
| Distance from home to local TB clinic (km) | | | | | p=0.003 |
| <10 | 188 | 24.1 | 69 | 21.3 | |
| 10-29 | 309 | 39.6 | 117 | 36.1 | |
| 30-39 | 149 | 19.1 | 51 | 15.7 | |
| ≥40 | 134 | 17.2 | 87 | 26.9 | |

111

112 **Table E2. Adjusted logistic regression of the association between temporal factors**
 113 **and suboptimal dosing implementation, adjusting for different confounder sets**

114 Adjusted models of the association between the temporal factors weekend, national holidays, and
 115 treatment phase and the outcome of non-adherence due to suboptimal dosing implementation. All
 116 models derive from Model 1. Each adjusts for the other temporal factors listed in the relevant stratum
 117 of the table plus age, sex and: distance from home to local TB clinic rather than rural-urban (Model
 118 1A), medical insurance rather than rural-urban (Model 1B), occupation rather than rural-urban (Model
 119 1C), both rural-urban and education level (Model 1D), rural-urban and total household income in last
 120 calendar year (Model 1E), county/district rather than rural-urban (Model 1F). 62,893 doses from 780
 121 individuals in the control arm of the original trial included. Random effect modelled on the initiation-
 122 continuation phase variable. Age and distance to TB included as linear variables, where relevant. CI-
 123 confidence interval, OR- odds ratio, TB- tuberculosis.

| Temporal factor | | OR (95% CI) |
|-------------------|--------------|---------------------|
| MODEL 1A | | |
| Weekend | Weekday | p<0.001 baseline |
| | Weekend | 1.14 (1.08-1.20) |
| National holidays | No | p<0.001 baseline |
| | Yes | 1.52 (1.39-1.65) |
| Phase | Initiation | p<0.001 baseline |
| | Continuation | 3.07 (2.68-3.51) |
| MODEL 1B | | |
| Weekend | Weekday | p<0.001 baseline |
| | Weekend | 1.14 (1.08-1.20) |
| National holidays | No | p<0.001 baseline |
| | Yes | 1.52 (1.39-1.65) |
| Phase | Initiation | p<0.001 baseline |
| | Continuation | 3.07 (2.68-3.51) |
| MODEL 1C | | |
| Weekend | Weekday | p<0.001 baseline |
| | Weekend | 1.14 (1.08-1.20) |
| National holidays | No | p<0.001 baseline |
| | Yes | 1.52 (1.39-1.65) |
| Phase | Initiation | p<0.001 baseline |
| | Continuation | 3.08 (2.69-3.53) |
| MODEL 1D | | |
| Weekend | Weekday | p<0.001 baseline |
| | Weekend | 1.14 (1.08-1.20) |
| National holidays | No | p<0.001 baseline |
| | Yes | 1.52 (1.39-1.65) |
| Phase | Initiation | p<0.001 baseline |
| | Continuation | 3.06 (2.67-3.50) |
| MODEL 1E | | |
| Weekend | Weekday | p<0.001 baseline |
| | Weekend | 1.14 (1.08-1.20) |
| National holidays | No | p<0.001 baseline |
| | Yes | 1.52 (1.39-1.65) |
| Phase | Initiation | p<0.001 baseline |
| | Continuation | 3.07 (2.69-3.52) |

126 **Table E2. continued**

127

| Temporal factor | | OR (95% CI) |
|------------------------|--------------|---------------------|
| MODEL 1F | | |
| Weekend | Weekday | p<0.001 baseline |
| | Weekend | 1.14 (1.08-1.20) |
| National holidays | No | p<0.001 baseline |
| | Yes | 1.52 (1.39-1.65) |
| Phase | Initiation | p<0.001 baseline |
| | Continuation | 3.14 (2.74-3.60) |

128

129

130 **Table E3. Adjusted odds ratios for the association between suboptimal dosing**
 131 **implementation and the initiation-continuation phase transition, stratified by county**

| | | Phase | |
|--------|------------|------------|------------------|
| | | Initiation | Continuation |
| County | Baiquan | baseline | 5.12 (3.69-7.11) |
| | Yilan | baseline | 2.64 (1.88-3.71) |
| | Rugao | baseline | 2.12 (1.44-3.13) |
| | Jianhu | baseline | 2.63 (1.83-3.78) |
| | Miluo | baseline | 3.31 (2.28-4.78) |
| | Yueyanglou | baseline | 2.48 (1.65-3.73) |
| | Fengjie | baseline | 4.18 (2.71-6.44) |
| | Shapingba | baseline | 4.05 (2.75-5.98) |
| | Jiangbei | baseline | 2.44 (1.73-3.45) |

132 Adjusted regression of the association between non-adherence due to suboptimal dosing
 133 implementation and the initiation-continuation phase transition (Model 1), stratified by county (Model
 134 1G). 62,893 doses from 780 individuals from the control arm of the original trial included. The stratum-
 135 specific ORs are adjusted for weekends, holidays, age, sex and county. Random effect modelled on
 136 the initiation-continuation phase variable. Age modelled as a linear variable. Results per cell
 137 presented as OR (95% CI). CI- confidence interval, OR- odds ratio
 138

139 **Table E4. Adjusted odds ratios for the association between suboptimal dosing**
 140 **implementation and holidays, stratified by county**

| | | Holiday | |
|--------|------------|----------|------------------|
| | | No | Yes |
| County | Baiquan | baseline | 0.94 (0.75-1.18) |
| | Yilan | baseline | 1.49 (1.18-1.88) |
| | Rugao | baseline | 1.43 (1.08-1.89) |
| | Jianhu | baseline | 1.39 (1.10-1.77) |
| | Miluo | baseline | 1.77 (1.37-2.28) |
| | Yueyanglou | baseline | 1.57 (1.17-2.11) |
| | Fengjie | baseline | 1.41 (1.02-1.94) |
| | Shapingba | baseline | 1.75 (1.35-2.27) |
| | Jiangbei | baseline | 2.37 (1.89-2.96) |

141 Adjusted regression of the association between non-adherence due to suboptimal dosing
 142 implementation and holidays (Model 1), stratified by county (Model 1H). 62,893 doses from 780
 143 individuals from the control arm of the original trial included. The stratum-specific ORs are adjusted
 144 for weekends, initiation-continuation phase transition, age, sex and county. Random effect modelled
 145 on the initiation-continuation phase variable. Age modelled as a linear variable. Results per cell
 146 presented as OR (95% CI). CI- confidence interval, OR- odds ratio
 147

148 **Table E5. Adjusted Cox regression models of the association between early**
 149 **suboptimal dosing implementation and discontinuation- sensitivity analysis**

150 Sensitivity analysis of the association between suboptimal dosing implementation in the initiation
 151 phase or month 1, and discontinuation. Model 3F examines the association between suboptimal
 152 dosing implementation in the initiation phase and discontinuation, adjusting for age, sex and
 153 county/district (as opposed to rural-urban in Model 3). It excludes individuals who discontinued in the
 154 initiation phase, leaving 740. Model 3G examines the association between suboptimal dosing
 155 implementation in the initiation phase and discontinuation whilst excluding individuals who
 156 discontinued after dose 86 (688 people in the model) and adjusts for the same confounders as Model
 157 3. Model 4F examines the association between suboptimal dosing implementation in month 1 and
 158 discontinuation, adjusting for age, sex and county/district (as opposed to rural-urban in Model 4). It
 159 excludes individuals who discontinued during month 1, leaving 775. Model 4G examines the
 160 association between suboptimal dosing implementation in month 1 and discontinuation whilst
 161 excluding individuals who discontinued after dose 86 (723 people in the model) and adjusts for the
 162 same confounders as Model 4. Age modelled as a linear variable in all models. CI- confidence
 163 interval.

| Temporal factor | Hazard ratio (95% CI) |
|----------------------------|-----------------------|
| MODEL 3F | |
| Initiation phase adherence | p=0.001 |
| ≥90% | baseline |
| 80-<90% | 1.17 (0.74-1.84) |
| <80% | 2.14 (1.46-3.14) |
| MODEL 3G | |
| Initiation phase adherence | p=0.001 |
| ≥90% | baseline |
| 80-<90% | 1.28 (0.78-2.09) |
| <80% | 2.40 (1.59-3.62) |
| MODEL 4F | |
| Month 1 adherence | p=0.002 |
| ≥90% | baseline |
| 80-<90% | 1.53 (1.05-2.22) |
| <80% | 2.06 (1.33-3.16) |
| MODEL 4G | |
| Month 1 adherence | p=0.001 |
| ≥90% | baseline |
| 80-<90% | 1.51 (1.00-2.28) |
| <80% | 2.39 (1.52-3.78) |

164

165 **REFERENCES**

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167 Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-
168 Randomised Trial. *PLoS Med* 2015;12:e1001876.

169

170 **FIGURE LEGENDS**

171 **Figure E1. Flow chart of participants**

172 Flow chart documenting participation from the original trial to this study. Side effects could
173 lead to temporary or permanent medication stoppage; in either instance, adherence data
174 were no longer collected.

175

Figure 1

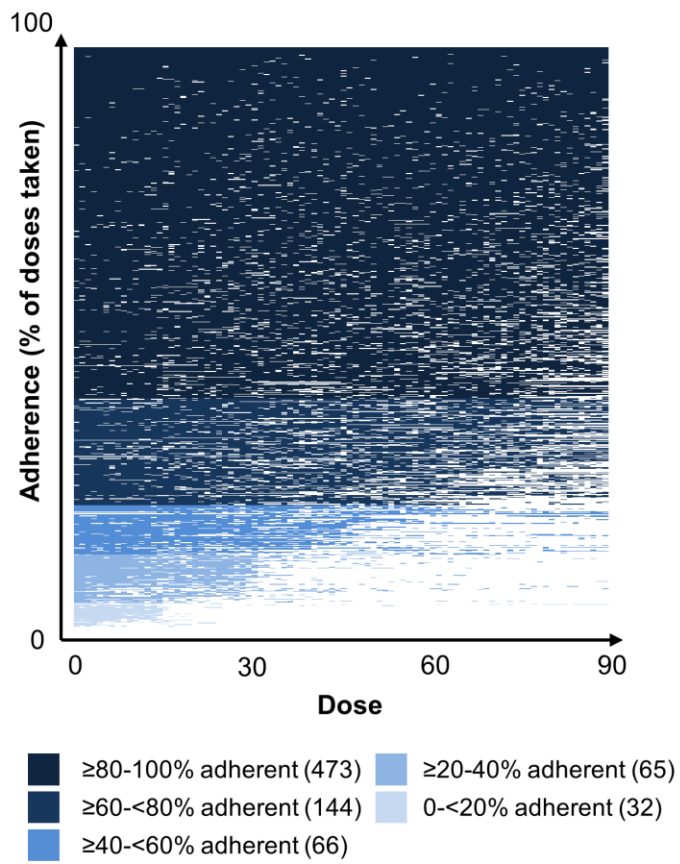


Figure 2

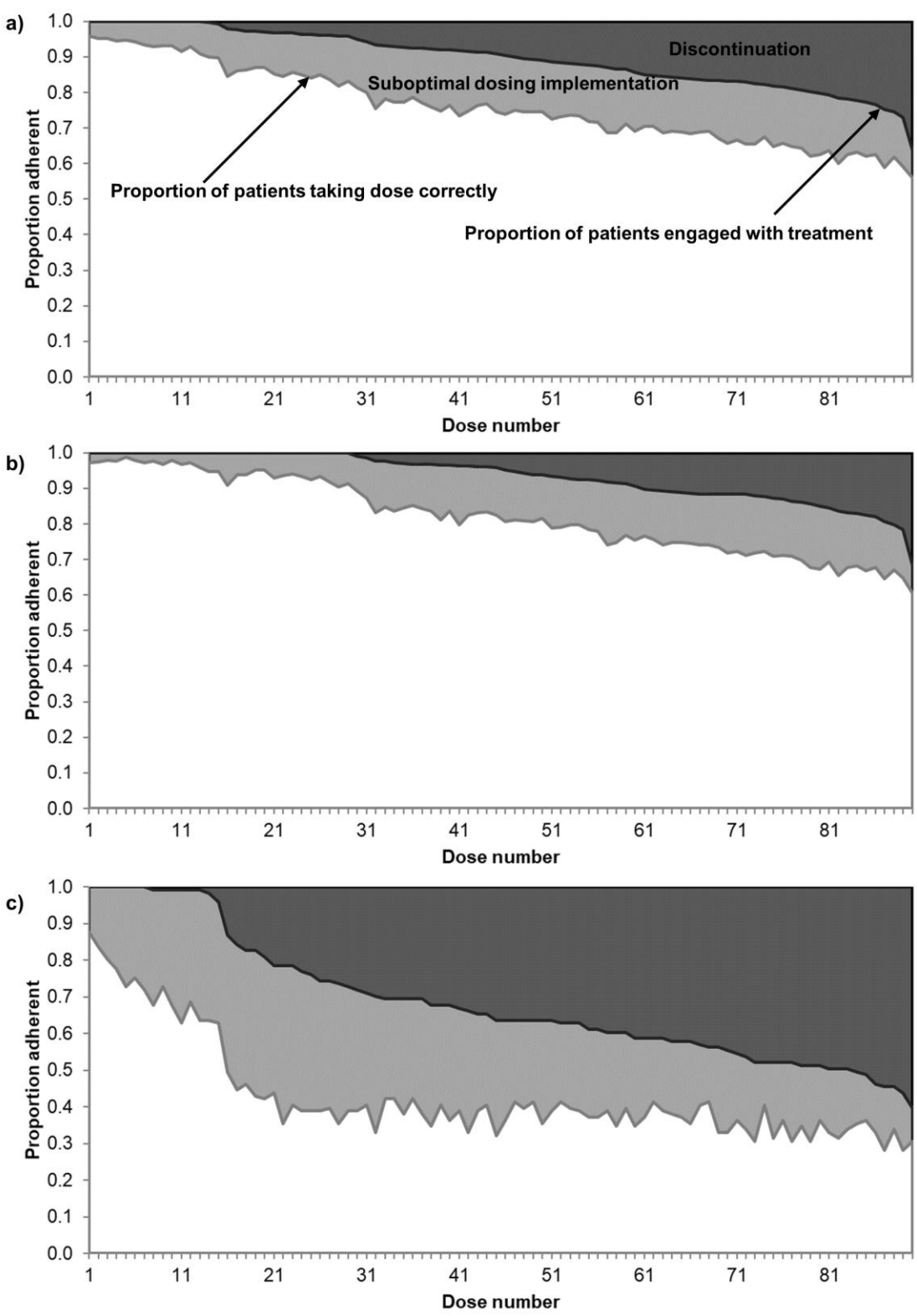


Figure 3

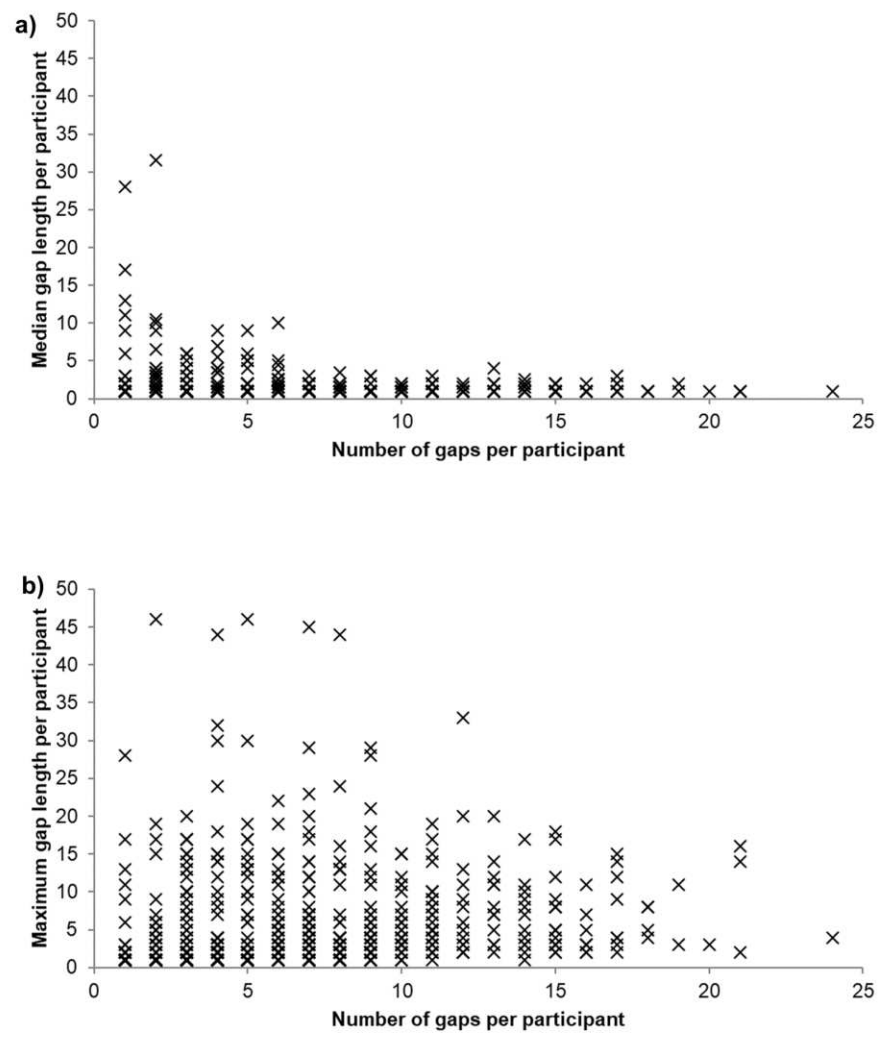


Figure E1

