

1 **Title:** The global burden of multi-drug resistant latent tuberculosis: recent trends and estimates using
2 mathematical modelling

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26 **Abstract**

27

28 *Background*

29 To end the global tuberculosis epidemic, latent tuberculosis infection (LTBI) must be tackled. All recommended
30 standard LTBI treatments contain drugs to which multi-drug resistant (MDR-) *Mycobacterium tuberculosis* are
31 resistant. Hence knowledge of the MDR-*M.tb* global LTBI burden will inform TB elimination policy-making.

32

33 *Methods*

34 By fitting a flexible statistical model to TB drug resistance surveillance and survey data collated by the World
35 Health Organisation, we estimated national trends in the proportion of new TB cases that were MDR-TB. This
36 was used as a proxy for the proportion of new infections due to MDR-*M.tb* and multiplied ARI trends from
37 previous LTBI estimate work to generate MDR-*M.tb* ARI trends. These were used within a new cohort model to
38 estimate changing levels of latent infection with MDR-*M.tb* (MDR-LTBI). We report global and national
39 prevalence of MDR-LTBI, as well as estimating recent infection levels and making predictions of the future
40 burden in 2035 and 2050.

41

42 *Findings*

43 We found that 19 [95% uncertainty interval (UI): 16-22] million individuals carried MDR-LTBI in 2014. This
44 represented 0.28% [95% UI: 0.24-0.31%] of the global population and 1.2% [95% UI: 1.0-1.4%] of all LTBI.
45 Country prevalence ranged from 0.002% to 3.8% of the population. In those aged less than 15 years, the
46 proportion of LTBI that is MDR was 2.9% [95% UI: 2.6-3.1%] (risk ratio compared to those over 15 years =
47 2.65 [95% UI: 2.11-3.25]). Recent MDR-*M.tb* infection meant that 1.9 [95% UI: 1.7-2.3] million individuals
48 globally in 2015 were at high risk of MDR-TB disease.

49

50 *Interpretation*

51 We estimate that three in every 1,000 people globally carry MDR-LTBI, resulting in one in every 83 individuals
52 with LTBI carrying MDR-*M.tb*, and one in every 34 in those less than 15 years old. With current trends the
53 proportion of LTBI that is MDR will increase, posing serious challenges for LTBI management, a cornerstone of
54 TB elimination strategies.

55

56 *Funding*

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58 **Introduction**

59

60 The complex natural history of the world's biggest infectious disease killer, *Mycobacterium tuberculosis* (*M.tb*),
61 means that for ultimate control those latently infected must be targeted.^{1,2} Currently, latent tuberculosis infection
62 (LTBI) is defined as “a state of persistent immune response to stimulation by *M. tb* antigens with no evidence of
63 clinically manifest active TB”.³ It has been estimated that 23% of the world's population could have LTBI and
64 that even without ongoing transmission after 2014, reactivation disease would overwhelm the 2035 End TB
65 Targets.⁴ Hence, understanding and targeting LTBI is a priority for TB elimination efforts,² as recognised by the
66 2018 UN High Level Meeting on TB.⁵

67

68 Antimicrobial resistance (AMR) is an increasingly serious threat to global public health.⁶ Multidrug-resistant
69 (MDR) strains of *M.tb*, which are resistant to both key first line TB drugs (rifampicin and isoniazid) cause
70 approximately one in four of all AMR deaths.⁷ In 2017, MDR-TB contributed to over 10% of TB deaths globally.⁸
71 MDR-TB patients experience low rates of appropriate diagnosis, low treatment success, and unacceptably long
72 treatment regimens (>18months). MDR-TB already accounts for a disproportionately large fraction of the financial
73 burden for TB control programmes. Preventing an increase of MDR-TB from a growing reservoir of MDR-LTBI
74 (i.e. LTBI caused by MDR-*M.tb* strains) is therefore critical for the success of any TB control programme.

75

76 Worryingly, MDR-*M.tb* are resistant to all currently recommended therapies prescribed to reduce the risk of
77 progression to active disease for people with LTBI who are not known contacts of an MDR-TB patient.³ The
78 priority population for LTBI testing and preventative therapy is currently household contacts of TB cases,⁹ likely
79 to be infected by their household member, but in high incidence settings, infection may also frequently occur
80 outside of the home.¹⁰ Due to such external transmission,¹¹ and low detection (<30%) of MDR-TB cases,⁸ a
81 substantial proportion of MDR-LTBI individuals will not have had recognized MDR-TB contacts and standard
82 preventive therapy could be less effective. All current LTBI diagnostics rely on measuring immune response,⁹
83 and cannot determine the strain, nor resistances, of any infecting *M.tb*. Hence, estimating MDR-LTBI levels can
84 help inform estimates of standard LTBI therapy efficacy. These estimates can also help guide usage of tailored
85 preventive treatment for contacts of MDR-TB patients^{3,12} and setting specific demand for new regimens (which
86 include levofloxacin and delamanid), currently being tested.¹³⁻¹⁵

87

88 In addition, as overall TB incidence and annual risk of infection (ARI) of TB decrease, there will be fewer people
89 infected with LTBI (DS or MDR) which is thought to partially protect against *M.tb* reinfection.¹⁶⁻¹⁸ If the TB
90 epidemic becomes increasingly driven by MDR transmission, the presence of an existing “protective” primary
91 DS-LTBI infection is less likely, which could further facilitate an increasing MDR-TB burden in the younger
92 generation.¹⁹ Hence, a decrease in total LTBI prevalence going forward may facilitate an increased proportion of
93 LTBI that is MDR.

94

95 No direct data on levels of MDR-LTBI exist as we cannot currently isolate any infecting *M.tb* bacteria and so
96 cannot test for resistance. Hence, a modelling approach is the only way to estimate this metric of TB burden. We
97 developed a new mathematical model which follows cohorts over time, applying historical ARIs estimated by a
98 previous study⁴ to track who becomes infected with LTBI. Capturing trends in the proportion of new TB cases
99 that are MDR as a proxy for the proportion ARI that is MDR,²⁰ allowed us to estimate trends in MDR-*M.tb*
100 infection risk and hence the proportion of each cohort with LTBI that carried MDR-*M.tb*. Using this we could
101 estimate global MDR-LTBI levels.

102

103 **Methods**

104

105 *Countries included*

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107 138 countries had both data on MDR levels in newly treated patients (survey or surveillance data) from the WHO
108 Drug Resistance Surveillance (DRS) Project, and were included in the original total LTBI estimates.⁴ These
109 countries account for 93% and 96% of the total incident TB and MDR-TB burden in 2016 respectively, and
110 include 28 of the 30 high MDR-TB burden countries.⁸ The two high MDR-TB burden countries that we excluded
111 had no WHO DRS data (Angola and the Democratic Republic of the Congo) and each contributed <1·5% of the
112 estimated global incident MDR-TB burden in 2016⁸. All details of country selection are given in the appendix.

113

114 *Trends in MDR-*M.tb* annual risk of infection (ARI)*

115

116 In order to estimate the burden of MDR-LTBI we needed trends in the annual risk of infection (ARI) with MDR-
117 *M.tb*. Previous work combined tuberculin skin test (TST) surveys with prevalence data and a revised Styblo rule
118 to generate ARI with all *M.tb* for 168 countries.⁴ A previous systematic review showed that levels of MDR-TB in
119 children and treatment-naïve adults with TB was a reflection of the current local MDR transmission.²⁰ Hence, we
120 used the proportion of MDR-TB in new TB cases reported to the WHO as a proxy for the proportion of ARI with
121 *M.tb* that was with MDR-*M.tb*. Fitting trends in the country-level proportions of MDR-TB in new TB cases (see
122 below) to the WHO DRS data was used to provide 200 samples from the posterior of potential fits. These were
123 multiplied by the total ARI with *M.tb* trend estimates from previous work,⁴ to give ARI with either *M.tb* strains
124 not resistant to both rifampicin and isoniazid (drug susceptible, DS-) and MDR-*M.tb*.

125

126 To capture the changing proportion of new TB cases that are MDR we fitted a flexible statistical model to the
127 WHO DRS data for MDR levels in new TB cases for each country over time using a Bayesian Markov chain
128 Monte Carlo (MCMC) approach with the *RStan* package in R (appendix).²¹ This model allows for increases,
129 stabilisation, and also subsequent decreases in the MDR proportion over time. In the absence of extensive
130 timeseries data (see appendix for a time plot of WHO data), this was fitted with informative priors, reflecting three
131 data-based assumptions about MDR trend characteristics, to constrain the potential pattern of MDR-TB increase.

132

133 Firstly, we assumed that it was very unlikely that detectable levels of MDR-TB could have appeared in any
134 country before 1970 (see appendix for references). To capture this time constraint, the model fitted, for each
135 country, a time when the proportion of new cases that were MDR-TB was assumed to appear at measurable levels.
136 The prior for this parameter was normally distributed with a mean of 1985 and a 95% range between 1970 and
137 2000. This matches a previous modelling study's assumption that "transmissible" MDR-*M.tb* strains arose 20-60
138 years before 2013.²²

139

140 Secondly, the rate of increase in proportion of new cases that were MDR was governed by two parameters (*b* and
141 *c*, see appendix) that were scaled to prevent too rapid an increase while still capturing the wide range of MDR
142 levels (including some very low rates of increase). Thirdly, we ensured that our model did not allow for a "peak
143 and crash" in the proportion with MDR-TB. The details for the choice of priors and plots of the trends generated
144 by these assumptions are given in the appendix.

145

146 *Estimating LTBI burden*

147

148 The estimates of both DS- and MDR-*M.tb* ARI were inputted into a new cohort model, tracking the proportion of
149 individuals at each age group infected with DS- or MDR-*M.tb* (appendix) from 1934 to 2014. The initial
150 conditions are calculated assuming a constant ARI pre-1934, and there is assumed to be no MDR-TB before 1960
151 (appendix). We present the estimates of LTBI in 2014 as this is the final time point in the ARI trends.⁴ Protection
152 against reinfection is taken to have a mean of 79%.¹⁶ We included all available WHO DRS data in the fitting
153 process, i.e. trends in proportion of new TB that is MDR used WHO MDR-TB data up to 2018 (single data point
154 from Togo).

155

156 Specifically, the burden we aim to characterise here is of the number of individuals with a persistent immune
157 response to stimulation by *M.tb* antigens without evidence of clinically manifested active TB.³ We report the
158 resistance status of the last infecting strain (e.g. MDR- or DS-*M.tb*) taking into account protection against
159 reinfection, ignoring dual infections, and, in the absence of a quantitative alternative, assuming lifelong
160 infection.

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162 *Recent levels of infection*

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We used model output to estimate the population infected with MDR-*M.tb* within the last two years (2013-2014) who would therefore be at a higher risk of progressing to active MDR-TB. These were chosen as these are the last two years for which we had modelled ARI trends from previous work.⁴

Risk ratio by age

We calculated the risk ratio for those under 15 years old having MDR-LTBI conditional on having LTBI, compared with those 15 or more years old. We chose 15 years old as the cut-off to match previous LTBI age segregated estimates and as this is a standard cut-off in TB natural history, as reflected in the WHO data.⁸

Burden of disease in 2035 and 2050

To estimate the contribution of these levels of MDR-LTBI to disease burden in 2035 and 2050, we assumed no *M. tb* transmission after 2014. Using UN Population Division demographic projections²³ we then estimated the MDR-LTBI burden in 2035 and 2050 and the level of MDR-TB disease (incidence) assuming a 0.03% per year remote activation rate, and explored this value in a sensitivity analysis.²⁴ We compared this to the WHO End TB targets of less than ten TB cases per 100,000 population by 2035, and the Stop TB target of less than one TB case per million population by 2050.¹

MDR-LTBI data coverage

To compare how well-informed by resistance data our MDR-LTBI estimates were, we used the cohort model to determine the proportion of LTBI in 2014 that originated in each 5-year time block in the past (e.g. 20% of those with LTBI in 2014 were infected in 2000 – 2005 in country X). The sum of all proportions from five year time blocks that had any WHO DRS data for that country gave the data coverage value (appendix). This gave a metric that combined the contribution of a time period to MDR-LTBI burden with whether data was present in that time to compare availability of MDR data by setting. The higher the value, the greater the overlap between contribution of a time period to MDR-LTBI burden and data availability.

193 *Sensitivity analyses*

194

195 There is an ongoing debate as to the fitness costs associated with the appearance of resistance within *M.tb.*^{25,26}

196 We undertook sensitivity analysis applying a 40% fitness cost²⁵ to the protection from reinfection (from 78% to

197 47%), and separately to the rate of reactivation (from 0.03% to 0.018%/year), in those with MDR-LTBI. We also

198 undertook a sensitivity analysis on trend shape: allowing for more flexible dynamics in MDR-ARI in a subset of

199 countries with sufficient data and a potential “peak and crash” in their proportion of all TB disease that was MDR

200 (see appendix for details).

201

202 *Role of the funding source*

203

204 The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing

205 of the report. The corresponding author had full access to all the data in the study and had final responsibility for

206 the decision to submit for publication.

207 **Results**

208

209 *Trends in levels of MDR-TB*

210

211 Model fits for all 138 countries gave estimates of the proportion of new TB cases that are MDR-TB that closely
212 matched the WHO data (see appendix for individual country trends). Examples of model fits for countries in the
213 WHO South-East Asia region are shown in figure 1. Here the substantial uncertainty associated with the lack of
214 data prior to 1990 can be seen, as well as the rising trend in the proportion of new cases that are MDR-TB across
215 all countries.

216

217 *Estimates of MDR-LTBI*

218 We estimate a global prevalence of MDR-LTBI in 2014 of 0.28% [95% uncertainty interval (UI): 0.24-0.31%]
219 (table 1, figure 2), representing 19 [95% UI: 16-22] million individuals with MDR-LTBI in 2014 (table 2). Of the
220 global LTBI burden, 1.2% [95% UI: 1.0-1.4%] is due to MDR-*M.tb*. Combined with our estimates of DS-LTBI
221 prevalence, total LTBI estimates match previous modelling,⁴ validating the new cohort model approach used here.

222

223 Geographical heterogeneity in the prevalence of MDR-LTBI was substantial, with the lowest estimate in the
224 Region of the Americas (0.05% [95% UI: 0.04-0.06%], table 1, figure 2). Variation in the estimates within the
225 West Pacific Region was large. Reflecting the data showing an increasing proportion of new cases being MDR-
226 TB, across the six regions we estimate that there has been a substantial increase in MDR-LTBI since 1990 (figure
227 2).

228

229 The estimates for prevalence of MDR-LTBI by country (figure 3 and appendix), show that most countries with
230 estimates have a prevalence of MDR-TB of less than 1%, whilst countries in Eastern Europe and Central Asia
231 have a prevalence of above 1.5%. Among the top-30 MDR burden countries, Kazakhstan had the highest
232 percentage of LTBI that is MDR at 17.5% [95% UI: 6.5-22.9%] (appendix). China (~6 million), India (~4 million)
233 and Russia (~1.8 million) had the highest absolute numbers of individuals with MDR-LTBI (appendix).

234

235 In children, the global percentage of LTBI that is MDR (<15 years old) is more than double that in the total
236 population at 2.9% [95% UI: 2.6-3.1%] (table 1), with the highest relative rate in the European region (14.1%
237 [95% UI: 13.1-15.2%] in children, vs. 2.8% [95% UI: 1.6-3.9%] in the total population). Aggregating by WHO
238 region shows that in all regions there is a peak in MDR-*M.tb* infection between 20 and 35 years old (figure 4).
239 The risk ratio for MDR-LTBI by age (i.e. the ratio of the proportion of those with LTBI that was MDR in those
240 < 15 years old vs. those > 15 years old) was 2.65 [95% UI: 2.11-3.25].

241

242 The number of individuals with recent MDR-LTBI infections in the past two years were estimated at 1.9 [95%
243 UI: 1.7-2.3] million individuals, or 0.03% [95% UI: 0.02%-0.03%] of the global population in 2014. This
244 population is at high risk of progressing to active MDR-TB. In children, we estimate that 0.6 [95% UI: 0.6-0.8]
245 million individuals aged < 15 years old were recently infected with MDR-TB in 2014.

246

247 Future projections of MDR-LTBI in 2035 remain high even assuming no ongoing transmission from 2015: 14
248 [95% UI: 12-16] million, decreasing to 11 [95% UI: 10-12] million by 2050 (see appendix for a map of the
249 prevalence). MDR-TB disease incidence from this latent pool would be 0.48 [95% UI: 0.42-0.53] per million per
250 year in 2035 and 0.34 [95% UI: 0.30-0.38] per million per year in 2050. These estimates do not exceed the 2035
251 WHO End TB or 2050 Stop TB targets (< one TB case per million) by 2050.¹

252

253 *Metric for data coverage*

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255 The mean and range of the metric for data coverage across all countries and model fits was 0.56 [0 - 1]. Fourteen
256 countries had median metric values of 1 suggesting that data was available within all contributing time periods.
257 Four countries had zero metric values as they only had data after 2014. The best data coverage for the 30 high
258 MDR burden countries was in Russia, Thailand and Uzbekistan (median metric values 0.87 – 0.99), whilst only
259 one had a median metric value below 0.25: Zimbabwe (appendix). The top four countries in terms of number with
260 MDR-LTBI (appendix) had median metric values above 0.5.

261

262 *Sensitivity analyses*

263

264 Reducing the protective effect of MDR-LTBI to reinfection by 40% resulted in a < 1% difference to all our
265 results on MDR-LTBI prevalence (appendix). The risk ratio for MDR-LTBI by age decreased slightly to 2.47
266 [95% UI: 2.03-2.97]. A 40% fitness cost affecting progression from MDR-LTBI to active disease (reactivation)
267 reduced TB disease incidence from the stable MDR-LTBI pool to 0.29 [95% UI: 0.25-0.32] and 0.20 [95% UI:
268 0.18-0.23] per million with MDR-TB in 2035 and 2050 respectively. Allowing for more flexible dynamics
269 resulted in a pre-1995 peak (i.e. before data was available) in the proportion of new TB that is MDR in the three
270 countries included (China, India and the USA). This increased overall MDR-LTBI estimates but had limited
271 impact on the MDR-LTBI estimates in those aged less than 15 years (appendix).

272 **Discussion**

273

274 We estimate that in 2014 the global prevalence of MDR-LTBI was 0·28% [95% UI: 0·24-0·31%] with substantial
275 variation by geography and age group. The proportion of LTBI that is MDR was 1·2% [95% UI: 1·0-1·4%], but
276 more than double this at 2·9% [95% UI: 2·6-3·1%] in children (< 15 years old). We estimated that if all
277 transmission stopped in 2015, reactivation cases from MDR-LTBI alone would not exceed the one per million
278 target for TB elimination by 2050, but would alone contribute approximately a third of the target.¹ For all WHO
279 regions we found that the levels of MDR-LTBI are increasing.

280

281 Our analysis suggests that MDR-LTBI prevalence currently peaks in 20 – 35 year olds. This reflects the
282 combination of lower LTBI prevalence in younger age groups due to lower cumulative exposure time, but an
283 increase in the proportion of *M.tb* infections that are MDR from the early 1990s. A high burden of MDR-LTBI in
284 children has been estimated previously, but the latter model assumed a constant ARI and did not consider other
285 age groups.²⁷ We showed that children have double the chance of having LTBI that is MDR compared to adults,
286 which is worrying given their higher rates of progression to disease and lower probability of appropriate diagnosis
287 or treatment for MDR-TB compared to adults.²⁸ For future MDR-TB burden, these children also represent a long-
288 persistent reservoir for MDR-TB disease, in the absence of substantial and effective roll-out of new LTBI
289 preventative therapy programmes. This higher burden is driven by the increasing proportion of ARI that is due to
290 MDR-TB, within the globally decreasing TB-ARI trend. Hence, children are more likely to be infected with MDR-
291 *M.tb* bacteria than the current generation of adults were. Indeed, the current generation of adults are partially
292 “protected” from the current TB-ARI by higher levels of DS-LTBI,¹⁶⁻¹⁸ and hence are less likely to have MDR-
293 LTBI. The public health implications of this are that, independently of MDR-TB contacts, LTBI infection cases
294 in children should be considered at a higher risk of being MDR.

295

296 Our top-ranked WHO global regions by MDR-LTBI prevalence (European and Western Pacific) in 2014 matched
297 the ranking for proportion of new cases with MDR-TB in the WHO 2018 Global TB report.⁸ These estimates,
298 alongside country level values, should help to guide preventative therapy in some settings: high levels of MDR-
299 *M.tb* infection in LTBI in high incidence settings may suggest that standard LTBI preventative therapy should be
300 given with even more caution to household contacts and that possible second-line therapies, such as those
301 currently under trial,¹³⁻¹⁵ should be considered.

302

303 Our estimated trends in MDR-LTBI at the WHO regional level were all increasing, as has been estimated
304 previously for China²⁹ and for isoniazid-resistant latent infection in Lesotho³⁰, despite WHO estimates suggesting
305 that MDR-TB incidence is currently relatively stable. Our aim was to characterize historical patterns of change in
306 MDR-ARI to inform MDR-LTBI burden rather than to determine current trajectories in MDR-TB incidence.

307

308 We have created a generalisable approach to combine historical data from country-level with generally
309 informative priors on MDR appearance to estimate global MDR-LTBI levels. We used informative priors to
310 capture the timings of isoniazid and rifampicin usage and limited rates of increase to better support the data
311 available. A strength of our approach is the inclusion of a range of trajectories in the proportion of new TB cases
312 that are MDR. Our model was also able to track infection by age, which highlights the increasing burden in
313 younger age groups. We also included sensitivity analyses around the impact of MDR on protection from
314 reinfection and rate of reactivation, finding that the former had little effect on our results whilst the latter reduced
315 our predicted MDR-TB incidence by approximately 40% (in line with the assumed parameter reduction). This
316 highlights the importance of determining this parameter for forecast analysis.

317

318 However, our analysis has several limitations. The first of these is the reliance on historical trends in proportion
319 of new TB cases that are MDR-TB when little data exists prior to 1990. By setting relatively informative priors
320 (e.g. very unlikely that MDR arose before 1970) and allowing for both quadratic and linear curves we believe we
321 have explored a reasonable area of potential MDR trend space and reflect this in our wide uncertainty ranges, but
322 this was fundamentally limited by the amount and precision of data. We explored this in a sensitivity analysis for
323 a limited set of high MDR burden countries where data indicated a potential peak in MDR-ARI before data was
324 available, by fitting more flexible spline models. While this had an impact on our results, it assumed MDR
325 transmission to rise rapidly from 1970 onwards and pushed the limits of the available data. It is clear, however,
326 that overall MDR-LTBI prevalence is sensitive to data and assumptions of pre-2000 trends, and future work could
327 include past trend determination, especially for China (possibly through phylogenetic analysis) as this contributed
328 most to the observed change in MDR-LTBI prevalence. Our data availability metric shows that most countries in
329 the top 30 MDR countries had good data availability (median metric values above below 0.5). New drug resistance
330 surveys or improved surveillance are needed to estimate levels of recent MDR-TB infection that could then be

331 used to update our MDR-LTBI estimates. When countries had both survey and surveillance data available, we
332 also did not treat the data differently (e.g. to account for potential underreporting in surveillance).

333

334 A second limitation is the homogeneity assumed in the model in terms of contact patterns, strain differences,
335 reactivation rates, spatial variation and population characteristics. By not including differences in mixing patterns
336 by age, we may have missed some age variation: age assortative mixing, combined with changing disease
337 presentation³¹ may result in further differences between children and adults. In terms of strain variation, we did
338 show that reduced reactivation rates for MDR-TB had a substantial impact on future MDR incidence suggesting
339 that strain variation differences in reactivation rates could drive differences in MDR incidence globally. For
340 example, future work could estimate variance in MDR-LTBI prevalence by HIV status, which may have
341 consequences for assumed fitness costs to resistance and hence greater levels of MDR-LTBI infection in HIV
342 positive populations. Similarly, we modelled, and averaged surveillance and survey data, at the national level,
343 which for some settings, such as the Russian Federation, may not be appropriate.

344

345 We also assume lifelong infection, despite the likelihood that self-cure is possible following *M.tb* infection.¹⁹
346 Indeed most of the LTBI estimates are based on TST and some TST positives may have cleared their *M.tb*
347 infection, suggesting that the reservoir of true *M.tb* infection for reactivation is smaller than estimated LTBI
348 prevalence (defined through persistent immune response).³² We also present recent infection levels which are
349 likely to cause the majority of current cases of MDR-TB disease. While our results may overestimate the
350 population carrying MDR-*M.tb*, this is accounted for in our estimates of MDR-TB disease driven by reactivation
351 from MDR-LTBI; the implications for global elimination targets are likely to be robust. We also only modelled
352 MDR, not all rifampicin resistance, as historical data was on MDR- not rifampicin-resistance levels.

353

354 A further complexity that we did not explore here was mixed infection as the dynamics of reactivation and mixed
355 strain disease are not fully understood, despite their importance.³³ LTBI was assumed to be with the last
356 successfully infecting strain (e.g. MDR- or DS-*M.tb*, taking into account protection against reinfection). However,
357 given the relatively low ARIs in past decades, potential mixed infections make up a low proportion of all MDR-
358 LTBI, and are unlikely to affect the total number of cases carrying MDR- or DS-LTBI.

359

360 Furthermore, in our main analysis we used a single study estimate for the level of protection against reinfection
361 progression conferred by LTBI status,¹⁶ despite there being other varying estimates available.^{17,18} This estimate
362 captures potential risk reductions in infection and/or of progressive TB dependent on LTBI status, which are
363 currently not possible to separate. We explored the impact of this parameter by lowering the protection again
364 reinfection for MDR-LTBI in our sensitivity analysis, finding a < 1% change. We did not include a sensitivity
365 analysis for all LTBI as this result, and the impact in previous work⁴ of reducing protection from the mean 79%
366 used here to 50% for all LTBI, was so small. The only impact seen in the previous work⁴, which was also
367 reflected in the slightly reduced risk ratio for MDR-LTBI by age in our sensitivity analysis, was on the age
368 distribution of recent infections, pushing there to be more in older age groups.

369

370 The broader, public health implications of this work are that evidence for the efficacy of current and potential
371 preventative therapies for those potentially carrying MDR-LTBI needs to be strengthened and the
372 recommendations possibly made context specific. Our estimates also provide some idea of the value of a
373 diagnostic test to differentiate between the resistance status of LTBI strains. In terms of future modelling work,
374 there is a need to quantify the rate and proportion of self-clearance of LTBI to better estimate the size of the
375 reactivation reservoir. For future transmission, it will be important to explore the impact of any fitness costs
376 conferred by resistance carriage in *M.tb* on natural history progression, as well as to better determine the trends
377 in MDR-*M.tb* ARI.

378

379 *Conclusions*

380 Our estimates suggest that one in every 83 individuals with LTBI carries an MDR-*M.tb* strain, resulting in nearly
381 three in every 1,000 people globally carrying MDR-LTBI. However, in children the number with LTBI that is
382 MDR is one in every 34 and will be higher still in close contacts of those with MDR-TB. Using WHO data on
383 proportion of new TB cases with MDR, we found that levels of MDR-LTBI are increasing in all WHO regions.
384 With these current trends, the MDR-LTBI proportion will only increase, posing serious challenges for LTBI
385 control, a cornerstone of TB elimination strategies.

386

387 **Contributors**

388 GMK, RMGJH and PJD conceived and designed the study. GMK led data analysis and modelling, and wrote a
389 first draft of the article. RMGJH, FM, GMK and PJD designed the methodology and critiqued the results. All
390 authors contributed to editing the final draft.

391

392 **Conflicts of interest**

393 We declare that we have no conflicts of interests.

394

395 **Ethics committee approval**

396 We required no ethics approval for this study.

397

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477 **Figure Legends**

478

479 **Figure 1: Median (black line) and 95% uncertainty range (blue shaded area) from 200 model fits to WHO**
480 **data (red) for the nine included countries from the WHO South-East Asia region.** Results for all countries
481 are given in the appendix. Note the varying y axis limits and that although we estimated MDR-LTBI burden in
482 2014 (hence the cut-off shown here) the model trend was fitted to all WHO DRS data.

483 **Figure 2: MDR-LTBI prevalence over time by WHO region.** The black line is the median, with shaded red
484 areas being the 95% uncertainty interval for each region from 200 model fits.

485 **Figure 3: Estimated population prevalence of MDR-LTBI (%).** Countries with no data shown in grey. The
486 same mapping at 2035 and 2050 is shown in the appendix.

487 **Figure 4: The percentage of the population in each age group for each of the six WHO regions with MDR-**
488 **LTBI.** The DS-LTBI levels are shown in the appendix. Error bars indicate 95% uncertainty interval.

489

490 **Tables**

WHO Region	DS-LTBI prevalence (%)	MDR-LTBI prevalence (%)	LTBI that is MDR (%)	LTBI that is MDR in <15 year olds (%)
African	22.1 [20.1-25.5]	0.23 [0.19-0.29]	1.0 [0.8-1.3]	2.3 [1.9-2.7]
Americas	10.6 [7.3-19.0]	0.05 [0.04-0.06]	0.5 [0.3-0.8]	3.3 [2.8-4.1]
South-East Asia	30.7 [27.7-34.5]	0.31 [0.23-0.41]	1.0 [0.7-1.3]	2.2 [1.9-2.6]
Eastern Mediterranean	16.4 [13.5-20.9]	0.14 [0.08-0.24]	0.9 [0.5-1.5]	2.9 [1.9-3.8]
Western Pacific	26.8 [17.8-39.2]	0.36 [0.26-0.49]	1.3 [0.7-2.2]	3.7 [3.3-4.1]
European	13.5 [9.9-19.8]	0.38 [0.32-0.44]	2.8 [1.6-3.9]	14.1 [13.1-15.2]
GLOBAL	22.9 [20.1-26.1]	0.28 [0.24-0.31]	1.2 [1.0-1.4]	2.9 [2.6-3.1]

491

492 **Table 1: Proportion of population infected with *Mycobacterium tuberculosis* of differing drug resistance**
493 **type, by WHO region, in 2014.** Brackets indicate 95% uncertainty interval.

494

495

WHO Region	Number with DS-LTBI (thousands)	Number with MDR-LTBI (thousands)
African	155,000 [141,000-179,000]	1,590 [1,310-2,010]
Americas	102,000 [70,700-183,000]	510 [418-624]
South-East Asia	584,000 [527,000-656,000]	5,810 [4,410-7,750]
Eastern Mediterranean	96,000 [78,900-122,000]	837 [481-1,410]
Western Pacific	493,000 [326,000-720,000]	6,620 [4,840-9,000]
European	122,000 [90,100-180,000]	3,440 [2,920-3,990]
GLOBAL	1,580,000 [1,380,000-1,800,000]	19,100 [16,400-21,700]

496

497 **Table 2: Number (thousands) of individuals infected with *Mycobacterium tuberculosis* of differing drug**
 498 **resistance type, by WHO region, in 2014.** Brackets indicate 95% uncertainty interval.