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2

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28 **SUMMARY**

29 The drug isoniazid (INH) is a key component of global tuberculosis (TB) control
30 programmes. It is estimated, however, that 16.1% of TB disease cases in former Soviet
31 Union countries and 7.5% of cases outside of those settings have non-multidrug resistant
32 (MDR) INH resistance. Resistance has been linked to poorer treatment outcomes, post-
33 treatment relapse and death, at least for specific sites of disease. Multiple genetic loci are
34 associated with phenotypic resistance, but the relationship between genotype and
35 phenotype is complex. This restricts the use of rapid sequencing techniques as part of the
36 diagnostic process to determine the most appropriate treatment regimens for patients. The
37 burden of resistance also influences the usefulness of INH preventative therapy. Despite
38 seven decades of the use of INH our knowledge in key areas- such as the epidemiology of
39 resistant strains, their clinical consequences, whether tailored treatment regimens are
40 required, and the role of INH resistance in fuelling the MDR-TB epidemic- is limited. The
41 importance of non-MDR INH resistance needs to be re-evaluated both globally and by
42 national TB control programmes.

43

44 **INTRODUCTION**

45 In 2013 the Director of the World Health Organization's (WHO) Global Tuberculosis (TB)
46 Programme described drug resistant TB as a 'ticking time bomb'. A need for 'visionary
47 political leadership' was identified.¹ Research and public health action in this area has been
48 dominated by multidrug resistant (MDR; resistance to both rifampicin (RMP) and isoniazid
49 (INH)) and extensively drug resistant (XDR; MDR plus resistance to a fluoroquinolone and
50 one or more of three second-line injectables) TB.

51

52 INH, first synthesised in 1912 in Prague,² is an effective first-line drug for the treatment of
53 active TB disease.³ A prodrug, INH is activated by the catalase-peroxidase KatG of
54 *Mycobacterium tuberculosis*. Following this, it binds InhA, an enoyl-acyl carrier protein
55 reductase and so blocks fatty (mycolic) acid synthesis, a key component of the bacterial cell
56 wall. In rapidly dividing bacteria INH is bactericidal, in slower dividing bacteria bacteriostatic.
57 The drug is thought to provide a high initial kill at the start of active TB treatment, after which
58 RMP largely takes over in terms of bactericidal activity and RMP and pyrazinamide (PZA)
59 act as sterilising drugs.⁴ From its earliest use as monotherapy for TB disease in the 1950s,
60 rapid and frequent development of resistance to INH was reported. Such observations
61 regarding INH and other drugs emphasised the need for combination regimens. INH,
62 streptomycin (STM) and p-aminosalicylic acid thus became the standard regimen for many
63 years before the development of the current short course of two months of INH, RMP, PZA
64 and ethambutol (EMB), followed by four months of INH and RMP.⁴⁻⁶ The 1950s also saw the
65 first studies of INH as a treatment for latent TB infections (LTBI),⁷ for which it is now a
66 standard mono- or combination therapy.^{8,9}

67

68 Resistance to INH has been associated with death in TB meningitis patients, where its role
69 in treatment is even more crucial as the only bactericidal agent to easily traverse the blood-
70 brain barrier.¹⁰ Additionally, a systematic review and meta-regression of trial data has
71 indicated that initial INH resistance increases the incidence rates of treatment failure and
72 relapse.¹¹ Given its relatively cheap price and low rates of adverse events,³ it is beneficial to
73 both health services and patients to be able to use INH. It is thus important to control the
74 spread of primary INH resistance and prevent the acquisition of secondary resistance.

75

76 In this paper, we pose ourselves- and our audience- a single question: is non-MDR INH
77 resistance of concern? Our answer depends upon a host of considerations- the burden of
78 INH resistance globally and regionally, the role of different resistance-causing mutations, the
79 extent to which resistance hinders treatment of active disease, whether tailored treatment
80 regimens are required, the relationship between INH resistance and MDR- which we

81 describe in the following sections. We conclude with how resistance can be prevented and
82 controlled, our perspectives on the implications of neglecting non-MDR INH resistance, and
83 the gaps and opportunities for public health.

84

85 **GLOBAL BURDEN OF INH RESISTANCE**

86 In 2011, Jenkins *et al.* produced the first analysis of global INH resistance data reported to
87 the WHO.¹² They found that, from 1994-2009, 131 unique settings (including countries and
88 sub-national regions) submitted such data at least once. This covered 56% of the world's
89 population, meaning that for nearly half of the global population data were not reported at
90 local or national levels (a key knowledge gap- see Table 1). Of the submitted nationwide
91 data, the former Soviet Union countries reported the highest percentages of TB cases with
92 INH resistance: 44.9% had some form of INH resistance (including mono-resistance and
93 MDR-TB) and 16.1% had non-MDR INH resistance without concurrent RMP resistance
94 (Figure 1). Across the rest of the world, excluding the former Soviet Union countries, 13.9%
95 of TB cases had some form of INH resistance (including mono-resistance and MDR-TB) and
96 7.5% INH resistance without RMP resistance. Between 1994 and 2013, the WHO estimated
97 that 9.5% of global TB cases had INH resistance without RMP resistance.¹³ The percentage
98 of paediatric TB disease with INH resistance reflects the percentage observed among new
99 adult cases.¹⁴ Around 12% of paediatric TB cases globally are estimated to have some form
100 of INH resistance, amounting to 120,000 new child cases annually. Additionally, Dodd *et al.*
101 have estimated that there are 166,000 new INH (without RMP) resistant infections in children
102 per year.¹⁵ As there are specific recommendations for the use of LTBI regimens, including
103 INH preventative therapy, in young children, such estimates have implications for the
104 effectiveness of these regimens.⁹

105

106 Time trend data are important to identify changes in the prevalence of INH resistance (Table
107 1). Jenkins *et al.* found that only 51 of the 131 settings above reported three or more
108 temporal data points and both upward and downward trends were observed, with no clear
109 global pattern.¹² Given the relevance of INH resistance¹² for people living with HIV (since they
110 are targeted for INH preventative therapy),¹⁶ the authors separately examined countries with
111 estimated adult HIV seroprevalences of at least 2%. In those countries, 7.3% of cases had
112 some form of INH resistance. Of concern, the only high HIV burden country with data
113 sufficient to analyse time trends (Botswana), had seen an increase in INH resistance. New
114 data from the South African drug resistance survey of 2012-14 (which are presented
115 nationally and by province) also indicate increasing prevalence.¹⁷

116

117

118 **RESISTANCE MUTATIONS**

119 Phenotypic INH resistance is associated with a number of mutations;¹⁸ at the time of writing
120 this review, 22 were documented by the TB Drug Resistance Mutation Database.^{19;20}
121 Determining the minimal number of mutations required to effectively detect INH resistance in
122 a clinical setting is thus complex.²¹ Lack of clarity about the association between specific
123 mutations, phenotypic resistance, and treatment outcomes hinders genotyping being used to
124 make rapid treatment decisions.^{22;23} *inhA* mutations are generally associated with lower
125 phenotypic resistance than *katG* mutations,^{24;25} but even within the same gene different
126 mutations can cause differing levels of phenotypic resistance. For example, *in vitro katG*
127 H270R mutations result in greater resistance levels than A162E, with the commonly studied
128 S315T mutation between the two.²⁵ Beyond the role of single point mutations, a strain's
129 genetic background contributes to the relationship between the genotype of resistance loci
130 and phenotypic resistance,²⁶ as does the presence of compensatory mutations e.g. in
131 *ahpC*.²⁷ It is important to note that *inhA* promoter mutations also affect susceptibility to
132 ethionamide, a core second line agent.²⁸

133

134 The distribution of different INH resistance mutations has been less well mapped globally
135 than general prevalence data, but estimates from an international collection of over 5,000
136 strains (bearing in mind issues due to clustering and sampling) suggest that 79% of non-
137 MDR INH resistant isolates have the *katG S315T* mutation (Manson *et al.*, currently under
138 review). Information on the distribution of mutations in non-MDR INH resistant TB is also
139 individually available from various settings e.g. China (49% of isolates found to have the
140 *katG S315T* mutation),²⁹ Ethiopia (60% *katG*),³⁰ Switzerland (57% *katG S315T*),²⁶ plus pan-
141 country studies e.g. Georghiou *et al.* (although this includes MDR strains).³¹ Given that some
142 mutations are less strongly linked to high-level phenotypic resistance (and thus theoretically
143 poor treatment outcomes with INH-containing regimens) than others, such data are critically
144 important for global planning (Table 1).

145

146 **THE INFLUENCE OF RESISTANCE ON TREATMENT OUTCOMES**

147 A high burden of non-MDR INH resistance is concerning in terms of TB control if the relative
148 and absolute likelihood of negative treatment outcomes is substantially higher for INH
149 resistant versus drug sensitive disease.

150

151 An early review of British Medical Research Council trials of different active TB treatment
152 regimens published in 1986 was optimistic on this front, contrasting 'the high success rate of
153 short-course regimens in the presence of initial resistance to isoniazid and streptomycin' to
154 'the response of the few patients with initial rifampicin resistance' (some of whom were

155 MDR).³² Results differed in a more recent and expansive systematic review and meta-
156 regression of trial data.¹¹ The authors found that, after controlling for the different
157 components of treatment regimens, initial INH resistance increased incidence rates of
158 treatment failure and relapse versus a baseline of pan-sensitive strains (incidence rate ratio
159 10.9 [95% confidence interval 5.9-20] and 1.8 [1.2-2.6], respectively). Some observational
160 studies from a variety of settings (with and without adjustment for treatment regimen and
161 other confounders) have found similar results, including the previously cited study examining
162 deaths in TB meningitis patients.^{10;33;34} Other studies have not found an association between
163 resistance and negative outcomes.^{35;36} A large retrospective cohort of patients receiving
164 short course chemotherapy from six countries was also less clear cut, showing an
165 association between INH resistance and the risk of treatment failure in retreatment cases
166 and weaker statistical evidence among new cases.³⁷

167

168 Different levels of phenotypic resistance might be expected to influence the success of INH-
169 containing regimen. Indeed, as stated by Van Deun *et al.* '[b]ecause of the large therapeutic
170 range of isoniazid, a fraction of patients may still benefit from the drug because the high
171 concentration achievable in tuberculosis lesions may overcome low-level resistance'.³⁸ Many
172 studies comparing treatment outcomes in individuals with high and low level phenotypic
173 resistance have not reported differences, although analyses are frequently not adequately
174 statistically adjusted and the methodology for determining resistance will also have been
175 influential.^{22;34;39-41} Published data on the influence of genotype are conflicting. In Vietnam,
176 an analysis without adjustment for treatment regimen suggested that *katG* but not *inhA*
177 mutations were associated with unfavourable treatment outcomes, and both mutations with
178 relapse in new patients.⁴² In an Indian cohort where patients were all prescribed the same
179 regimen *katG*, but not *inhA* mutations, were associated with poor treatment outcomes in an
180 unadjusted analysis (and certain *inhA* mutations were more associated with cure than
181 others).⁴³ Other analyses have indicated that there is no difference in treatment outcomes by
182 mutation, although again are often not appropriately adjusted.^{30;41;44}

183

184 On balance, therefore, the precise link between INH resistance and treatment outcomes is
185 unclear, with disagreements likely due to how well studies statistically adjusted for
186 confounding. Resistance is likely to be detrimental at least for certain sites of disease and
187 without adapted treatment regimens. Further work is required (Table 1).

188

189 **TAILORING TREATMENT REGIMENS IN THE PRESENCE OF RESISTANCE**

190 If INH resistant TB has a greater likelihood of negative treatment outcomes than drug
191 sensitive disease, then specific effective regimens are required. Substituting for INH is

192 clearly not ideal, given its low cost and frequency of adverse events. Global guidance does,
193 however, often reflect the need for adjusted regimens, albeit without a consensus on the
194 best approach to take (Table 2). A common theme of guidelines is the recognition of
195 knowledge gaps requiring further research (Table 1).

196
197 In a recent systematic review and network meta-analysis by Stagg *et al.* of randomised
198 controlled trials of different treatment regimens for non-MDR INH resistant TB, 59 studies
199 were found for inclusion.⁴⁵ A regimen category of RMP-containing regimens using fewer than
200 three effective drugs at four months, in which RMP was protected by another effective drug
201 at six months, and RMP was taken for six months, was used as the baseline for a network
202 meta-analysis (this included the WHO population level recommendation [Table 1]).
203 Extending the duration of RMP to more than six months and increasing the number of
204 effective drugs at four months to three or more lowered the odds of unfavourable versus
205 favourable outcomes in a fixed-effects model (odds ratio 0.31 [95% credibility interval 0.12-
206 0.81]). This was the only regimen category where the credibility interval did not cross the
207 null, however, in a random-effects model all estimates did so. In both models, this regimen
208 category (RMP containing, three or more effective drugs at four months, RMP protected by
209 another effective drug at six months, RMP taken for more than six months) and two others
210 (RMP containing, fewer than three effective drugs at four months, RMP taken for six months;
211 RMP containing, fewer than three effective drugs at four months, RMP taken for more than
212 six months) consistently ranked in the top three out of the 11 included, albeit with much
213 uncertainty.

214
215 Menzies *et al.* also reviewed randomised controlled trials for the treatment of INH
216 monoresistant TB in a paper published in 2009,⁴⁶ with the aim of assessing the effectiveness
217 of the 2008 WHO 'retreatment' regimen (two months of STM INH RMP PZA EMB followed
218 by one month of INH RMP PZA EMB and then five months of INH RMP EMB) in patients
219 with INH resistant disease. Despite the two reviews having very different inclusion and
220 exclusion criteria the findings were similar, with the Menzies *et al.* review concluding that a
221 RMP duration of two months or less, having few drugs in the intensive phase, and therapy
222 being delivered twice weekly throughout increased both treatment failure and relapse rates,
223 with additional factors influencing one or other measure. It should be noted that, due to a
224 lack of appropriate trials, Menzies *et al.* were unable to determine the efficacy/effectiveness
225 of the specific WHO retreatment regimen for INH resistant TB. However, heterogeneous
226 cohort study data indicated treatment failure in 18-44% of cases with INH resistance versus
227 0.7-27% of patients with pan-sensitive strains.

228

229 High-quality data are lacking on the influence of treatment adherence, the use of
230 combination pills, and the presence of different resistance mutations on the efficacy of
231 regimen recommendations. Furthermore, people metabolise INH at different speeds
232 depending upon their acetylator phenotype. This may also influence regimen efficacy, as fast
233 acetylation can lead to less stable serum levels of INH, resulting in worse outcomes with INH
234 containing regimens.⁴⁷

235

236 Additionally, neither of the two cited reviews specifically looked at regimens for children. For
237 drug sensitive TB in children without HIV co-infection and in areas of a 'low' prevalence of
238 INH resistance the WHO recommends a three-drug two-month intensive phase of INH, RMP
239 and PZA, followed by four months of INH RMP.⁴⁸ In the presence of INH resistance, or if the
240 child is diagnosed where there is a 'high background prevalence of isoniazid resistance',
241 WHO state that EMB should be added during the intensive phase and that '[f]or patients with
242 more extensive disease, consideration should be given to the addition of a fluoroquinolone
243 and to prolonging treatment to a minimum of 9 months'. Indeed, observational studies
244 suggest that fluoroquinolones may play a role in treating both adult and childhood
245 disease,^{39,49} at least where it is extensive (Table 1).

246

247 **FROM INH RESISTANCE TO MULTIDRUG RESISTANCE**

248 Aside from the implications of INH resistance on treatment, if non-MDR INH resistance is the
249 key precursor to MDR (as opposed to non-MDR RMP resistance) and the risk of progression
250 from INH resistance to MDR is high enough, then the control of such strains is very
251 important. The relative prevalence of different resistance patterns across settings can be
252 informative here, as can studies of the particular INH resistance mutations commonly
253 observed in MDR strains. At a population level, evidence can also be provided through
254 phylogenetic studies calculating the temporal order in which mutations occur. If we are
255 convinced that INH resistance precedes RMP resistance then the risk/rate of a strain
256 becoming MDR once INH resistant becomes critical. This is calculable through clinical trials
257 and prospective observational studies analysed at the individual level. We examine each line
258 of evidence in turn in the following paragraphs.

259

260 Globally, the proportion of RMP resistant strains that are MDR is higher than the equivalent
261 proportion of INH resistant strains. An analysis of aggregate WHO data from 125 settings
262 and several years has estimated that 87% of RMP resistant isolates are MDR.⁵⁰ By
263 comparison, using available nationwide data from Jenkins *et al.*,¹² we calculated an average
264 (weighted by the population in each country) of 39% of INH resistant strains being MDR. (It
265 should be noted that this estimate relies upon reported data that is two or more decades old

266 in some cases.) Such patterns likely reflect at least one of three things- the relatively high
267 INH resistance mutation rate as opposed to that for RMP;⁵¹ that strains, once RMP resistant,
268 rapidly acquire additional INH resistance; or that INH resistance is generally the first step to
269 MDR.

270

271 Given that *katG* mutations are generally associated with greater phenotypic resistance than
272 *inhA* mutations, if INH resistance is the first step to MDR it might be assumed that the former
273 will be more common in MDR strains than the latter. Studies in various settings (of which the
274 cited are a few) have demonstrated this to be the case,^{26;29;30;52-58} (including enrichment of
275 *katG* mutations in MDR versus non-MDR INH resistant strains^{21;26;29;30;59}). The 'spectrum' of
276 mutations observed in MDR strains varies from setting to setting, however, and may be
277 linked to the dose of INH used for treatment⁵⁷ and the clonal spread of different mutations.
278 The prevalence of different mutations will also reflect relative fitness, which is a complex
279 trait⁶⁰ that may additionally be related to the speed at which bacteria are growing.⁶¹

280

281 A systematic review and meta-regression of trial data published by Menzies *et al.* in 2009
282 examined the question of whether initial INH resistance is associated with increased rates of
283 additional resistance.¹¹ Incidence rates of acquired drug resistance were found to increase
284 5.1 times in patients with INH resistant disease versus drug sensitive disease (95%
285 confidence interval 2.3 to 11.0) after treatment regimen was controlled for. This study
286 examined any additional resistance to the drugs received, rather than looking specifically at
287 the transition to MDR, however (Table 1). Although there are randomised controlled trials
288 that specifically document RMP resistance arising in INH resistant versus drug sensitive
289 patient populations by regimen both during and after treatment, data are relatively minimal.⁶²⁻
290 ⁷⁴ Within these trials (all of which used RMP in all arms) the development of RMP resistance
291 almost exclusively occurred in less than 1% of drug sensitive disease patients across failure
292 and relapse. In most instances this was also true for INH resistant disease. Notable
293 exceptions in the latter population (high risk of progression during treatment [8-31%], but not
294 at relapse) occurred when regimens consisted of INH and RMP alone (plus minimal STM, or
295 STM in the presence of STM co-resistance). One trial in HIV positive individuals documented
296 a much higher risk of developing RMP resistance in drug sensitive patients during both
297 treatment failure and relapse and INH resistant patients during treatment failure, but this may
298 have been because patients were repeatedly re-infected during treatment.⁷³ Although the
299 findings above do not include trials where a comparator drug sensitive disease group was
300 missing or where information was not presented by treatment regimen, it does give an
301 indication of a generally low risk of the development of additional resistance. By comparison,
302 observational studies without a comparator drug sensitive disease group have documented

303 highly differing estimates of the likelihood of INH resistant disease progressing to MDR,
304 ranging from <1-10%.^{39,44;75-78} In both randomised controlled trials and observational studies,
305 estimates will be highly regimen dependent.

306

307 Rapid and cheap whole genome sequencing makes analysing the progressive gain of
308 resistance mutations at the population level using phylogenetic trees an achievable
309 approach.⁷⁹ A recent study of samples from a particular *Mycobacterium tuberculosis* clone
310 from KwaZulu-Natal in South Africa indicated that INH resistance (*katG*) mutations arose
311 approximately 30 years earlier than RMP resistance.⁸⁰ A previous study from Argentina also
312 placed *katG* mutations prior to *rpoB* ones, albeit with a much shorter (3 year) gap and
313 overlapping confidence intervals.⁸¹ Other studies using different typing techniques (including
314 phenotyping) at the individual or population level have similarly suggested that INH
315 resistance arises before RMP resistance.⁸²⁻⁸⁵ Results at the population level may, however,
316 simply reflect when the different drugs were introduced and the more rapid mutation rate to
317 INH resistance. A recent study across five continents, however, not only indicated that in
318 96% of MDR strains INH resistance was observed before RMP resistance, but also that this
319 was independent of lineage, where strains were sampled from, and the time when resistance
320 arose i.e. INH resistance predated RMP resistance even after both drugs were in use
321 (Manson *et al.*, currently under review).

322

323 Saunders *et al.* have proposed that INH resistance might precede RMP resistance in the
324 development of MDR because the selective pressure of RMP is smaller than that of INH,
325 thus RMP resistant strains are more likely to be killed by INH than INH resistant strains by
326 RMP.⁸⁴ The INH resistant strains thus survive and develop additional resistance during
327 substandard treatment. A higher mutation rate in strains with *katG* mutations in the presence
328 of oxidative stress has also been suggested as a potential explanation, although evidence is
329 lacking.⁸⁶

330

331 **HOW CAN WE PREVENT INH RESISTANCE?**

332 The prevention of INH resistance falls into two categories- the need to control the spread of
333 INH resistant strains (primary resistance) and the need to prevent patients developing
334 secondary resistance.

335

336 The prevention of primary resistance relies upon ensuring that INH sensitivity is documented
337 in all patients- preferably using rapid techniques- who are promptly placed on an effective
338 treatment regimen. Importantly, modelling work has indicated no evidence that the *katG*
339 S315T mutation (for example) impairs virulence or transmissibility.⁸⁷ Effective treatment

340 regimens for INH resistant LTBI (which may need to be different to standard regimens) are
341 also important, including knowing when the population level prevalence of resistance is
342 sufficient to require such regimens to be used nationally as opposed to only in contacts of
343 INH resistant disease cases.

344

345 Guidance and studies on the treatment of drug resistant LTBI infections are few and far
346 between, with work focussing on MDR. Early reports exist of INH prophylaxis failing in
347 contacts of patients with INH resistant TB, but such studies do not contain good comparison
348 estimates of the failure of prophylaxis in individuals with drug sensitive infections.⁸⁸⁻⁹⁰ Neither
349 the WHO nor (for example) the National Institute for Health and Care Excellence, UK make
350 explicit recommendations regarding the treatment of contacts exposed to INH resistant TB
351 (including for children).^{9;48;91} The American Thoracic Society and Centers for Disease Control
352 and Prevention, USA recommend a four month regimen of RMP for such individuals (six
353 months for children),⁹²⁻⁹⁴ unless they are 'HIV-infected persons taking some combinations of
354 [antiretroviral therapy]'. This recommendation was based upon a small number of
355 publications.^{89;95-98} Of note, three to four months of RMP is the only non-INH containing
356 regimen currently recommended for LTBI by the WHO.⁹ In the absence of clearer evidence
357 from trials and observational studies about whether INH-containing regimens are suitable for
358 INH resistant LTBI (Table 1), data may also be gleaned by comparing the results of studies
359 undertaken in settings of different INH resistance prevalences.

360

361 In order to estimate the critical prevalence of INH resistance before RMP LTBI regimens
362 should replace nine months of INH, a modelling study was undertaken in migrant children.⁹⁹
363 From a cost/benefit perspective, the regimen switch was recommended for children
364 originating from settings where the prevalence is at least 11%. The study was, however,
365 criticised by other researchers, particularly for its assumptions regarding the relative
366 effectiveness of different LTBI regimens.¹⁰⁰

367

368 The prevention of secondary resistance largely relies upon ensuring appropriate adherence
369 to treatment, responsive monitoring of patient progress, and ensuring good access to drugs
370 to avoid regimen breaks.¹⁰¹ Higher strength pills (to reduce the number of tablets a patient
371 takes at any one time) and combination pills may improve adherence and ensure adequate
372 dosing. Regimens- particularly if they are intermittent- may need to be tailored to acetylation
373 phenotype.¹⁰² Additionally, the role of INH preventative therapy in producing INH resistant
374 LTBI has been debated.^{103;104} Of note, INH resistant disease in this instance would be
375 incorrectly classified as having primary drug resistance.

376

377 **CONCLUSION**

378 INH is an important drug for the control of TB that we cannot afford to lose. It is cheap,
379 effective, has a low rate of adverse events, and cannot currently be substituted by an equal
380 alternative. Non-MDR INH resistance is surprisingly prevalent globally, especially in former
381 Soviet Union countries. Resistance may increase the likelihood of negative treatment
382 outcomes, post-treatment relapse, and death at least for certain sites of disease and with
383 specific regimens. The incidence of non-MDR INH resistance (which is higher than that of
384 MDR-TB) may limit the effectiveness of INH preventative therapy at the population level.

385

386 There are many knowledge gaps regarding INH resistant TB (Table 1). The most critical of
387 these is perhaps the exact link between resistance-associated mutations, phenotypic
388 resistance and active TB treatment outcomes. Rapid sequencing technologies make
389 genotyping highly attractive as part of a pipeline to rapidly make patient-level treatment
390 decisions, thus these links are crucial. Such technologies will, however, be hindered by the
391 number of mutations associated with INH resistance. Better data on the burden of INH
392 resistance globally is also required in order to ascertain whether INH preventative therapy
393 policies should be adjusted. Importantly, none of the gaps highlighted would seem complex
394 to fill.

395

396 National interest in non-MDR INH resistance is context-specific, depending upon the extent
397 to which a country is concerned about further resistance arising, the accessibility of first line
398 drug sensitivity testing, the availability of alternative regimens for both LTBI and active
399 disease, and budgetary limitations (including how much of a country's resources are
400 currently being spent on MDR). The WHO reflected this in their treatment guidelines- the
401 recommendations of which are tailored to whether the local burden of resistance is deemed
402 'high'- stating 'WHO does not intend to establish thresholds for low, moderate or high levels
403 of prevalence of isoniazid resistance: [National Tuberculosis Programmes] will establish
404 definitions for their own countries.'⁴⁸

405

406 Accurate drug sensitivity testing for all patients is critical for global TB control.¹ As use of
407 GeneXpert becomes more widespread, countries may cease testing for INH resistance, as
408 samples negative for RMP resistance (used as a proxy for MDR) will undergo no further
409 sensitivity testing. The implications of this are two-fold: even less data to estimate INH
410 prevalence and a risk of inadequate treatment of non-MDR INH resistant disease, leading to
411 further (undetected) transmission. This picture will change should GeneXpert XDR, which
412 includes testing for at least some INH resistance genes, be trialled successfully.¹⁰⁵ A
413 modelling study using data from India has suggested a limited role for rapid INH resistance

414 testing on transmission, however.¹⁰⁶ Comparatively, in Peru, GeneXpert in its current form is
415 not favoured as a diagnostic due to the perceived importance of the country's burden of INH
416 resistant strains.¹⁰⁷

417

418 Readers may argue that non-MDR INH resistance has apparently been neglected for many
419 years without too disastrous a consequence, and the fact that the proportion of non-MDR
420 disease cases who fail treatment is low globally, despite the current prevalence of
421 resistance, means that we need not be too concerned. This may well be the case in many
422 settings and, indeed, we do not recommend that INH resistance be given priority over MDR
423 and XDR-TB for research funding. Nevertheless, as a stepping stone to MDR, a high or
424 increasing prevalence of INH resistance is concerning, and if tracked adequately in the past
425 this may have aided the prevention of the MDR-TB epidemic.

426

427 At the beginning of this article, we posed a question- to what extent is INH resistance a topic
428 of concern? Our review of the literature suggests that non-MDR INH resistance has been
429 neglected, and that this lack of focus needs to be addressed as an important means of
430 controlling global TB.

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432

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446

447 **AUTHOR CONTRIBUTIONS**

448 HRS and HEJ conceived and designed the work, collated the evidence and drafted the
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821 TABLES

822 Table 1: Summary of knowledge gaps for isoniazid resistant tuberculosis

Area	Missing information	Potential data sources
Prevalence of phenotypic INH resistance	44% of the world's population is not covered by prevalence data that could be included at the time of Jenkins <i>et al.</i> ¹² Many reported estimates are old. Temporal trend data are often missing.	(Repeated) cross-sectional studies, surveillance data
Phenotypic versus genotypic resistance	How do specific resistance-associated mutations relate to phenotypic resistance?	Cross-sectional microbiological studies
Relative prevalence of resistance mutations	How are the different INH resistance-causing mutations distributed globally? Does this differ within specific population groups e.g. populations deemed at high risk of MDR disease?	Systematic review of available literature, cross-sectional studies
Treatment outcomes in active disease	How do phenotypic resistance (measured in different ways) ²² and genotypic resistance influence treatment outcomes and the likelihood of relapse?	Systematic review of available literature
Treatment regimens for active disease*	Are regimens with an increased dose of INH effective in instances of low-level phenotypic resistance? What are the best regimens in children? At what resistance prevalence threshold should recommendations to use specific regimens be made?	Randomised controlled trials, mathematical modelling, health economics
Progression to MDR	What is the absolute risk of INH resistant strains becoming MDR during treatment? How does this compare to drug sensitive disease? How does this relate to treatment regimen?	Systematic review of available literature, cohort studies

LTBI treatment regimens	How effective are currently recommended LTBI treatment regimens for INH resistant infection? Are other regimens required, including for children? At what population-level of INH resistance is it best to avoid INH preventative therapy?	Randomised controlled trials, mathematical modelling, health economics
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823 *The American Thoracic Society,¹⁰⁸ National Institute of Health and Care Excellence, UK⁹¹
824 and World Health Organization⁵ all have their own recommendations on this topic. The
825 American Thoracic Society has recently updated their guidance on the treatment of drug
826 sensitive disease, but at the time of writing new guidelines for treating drug resistant disease
827 have not been released. INH- isoniazid, LTBI- latent tuberculosis infection, MDR- multidrug
828 resistance
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831 **Table 2: Global guidance on treating isoniazid resistant tuberculosis disease in adults**

Issuer of guidance	Treatment regimen(s) recommended	Reference(s)
World Health Organization	<p>Two sets of guidance, one on the basis of background levels of INH resistance and non-availability of drug sensitivity testing before the continuation phase of treatment, the other when individual-level drug sensitivity testing is available. Where background levels are deemed ‘high’ among new TB patients and INH susceptibility testing results are not available before the continuation phase two months of INH, RMP, PZA and EMB followed by four months of INH, RMP and EMB are recommended. The threshold for ‘high’ levels is not defined.⁴⁸</p> <p>In the presence of individual-level drug susceptibility results, recommendations are made depending upon the non-MDR INH resistance pattern found. For example, six to nine months of RIF, PZA and EMB (plus or minus a fluoroquinolone) for INH-monoresistant or INH and STM-resistant disease.</p>	5;109
American Thoracic Society	Six month regimen of RMP, PZA and EMB (plus a fluoroquinolone for extensive disease).	108
National Institute of Health and Care Excellence, UK	Nine month regimen (10 months where disease is extensive) of two months of RMP, PZA and EMB, then seven months of RMP and EMB.	91

832 EMB- ethambutol, INH- isoniazid, PZA- pyrazinamide, RMP- rifampicin, STM- streptomycin

833

834 **FIGURE LEGENDS**

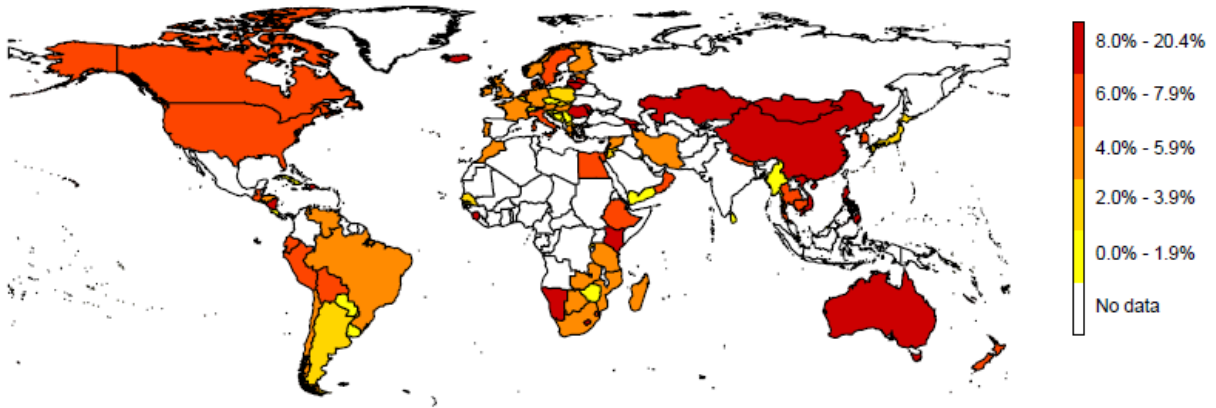
835 **Figure 1: Percentage of incident tuberculosis cases with isoniazid resistance but not**
836 **rifampicin resistance, 1994-2009**

837 World map showing the percentage of incident tuberculosis disease that was isoniazid
838 resistant, but not multidrug resistant, 1994-2009. National level data only, sourced and
839 analysed as per Jenkins *et al.*¹² Where countries submitted repeated estimates most recent
840 data shown only. White areas did not report national data during the time period in question.

841

842 **FIGURES**

843 **Figure 1: Percentage of incident tuberculosis cases with isoniazid resistance but not**
844 **rifampicin resistance, 1994-2009**



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