Title: Isoniazid resistant tuberculosis- a cause for concern?

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Running header: Isoniazid resistant tuberculosis

Word count (summary): 174

Word count (main text): 4,498

References: 109

Tables: 2

Figures: 1

Keywords: monoresistance, epidemiology, public health

SUMMARY

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

INTRODUCTION

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

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

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

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

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

GLOBAL BURDEN OF INH RESISTANCE

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

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

RESISTANCE MUTATIONS

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

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

THE INFLUENCE OF RESISTANCE ON TREATMENT OUTCOMES

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

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

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

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

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

TAILORING TREATMENT REGIMENS IN THE PRESENCE OF RESISTANCE

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

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

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

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

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

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

FROM INH RESISTANCE TO MULTIDRUG RESISTANCE

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

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

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

Given that *katG* mutations are generally associated with greater phenotypic resistance than *inhA* mutations, if INH resistance is the first step to MDR it might be assumed that the former will be more common in MDR strains than the latter. Studies in various settings (of which the cited are a few) have demonstrated this to be the case,[26;29;30;52-58] (including enrichment of *katG* mutations in MDR versus non-MDR INH resistant strains[21;26;29;30;59]). The 'spectrum' of mutations observed in MDR strains varies from setting to setting, however, and may be linked to the dose of INH used for treatment[57] and the clonal spread of different mutations. The prevalence of different mutations will also reflect relative fitness, which is a complex trait[60] that may additionally be related to the speed at which bacteria are growing.[61]

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

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

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

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

HOW CAN WE PREVENT INH RESISTANCE?

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

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

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

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

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

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

CONCLUSION

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

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

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

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

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

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

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

ACKNOWLEDGEMENTS

The authors wish to acknowledge Professor Andrew Nunn's valuable comments on an early version of this manuscript.

FUNDING

This report is independent research supported by the National Institute for Health Research (Post Doctoral Fellowship, Dr Helen Stagg, PDF-2014-07-008). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. This work was supported by the U.S. National Institutes of Health (US NIH K01AI102944 award to HEJ). The content is solely the responsibility of the authors and does not necessarily represent the views of the U.S. National Institute of Allergy and Infectious Diseases or the U.S. National Institutes of Health.

AUTHOR CONTRIBUTIONS

HRS and HEJ conceived and designed the work, collated the evidence and drafted the original manuscript. All authors interpreted the evidence, revised the manuscript critically for intellectual content, and gave their approval of the manuscript.

CONFLICT OF INTERESTS

HRS declares funding from the National Institute for Health Research (NIHR), UK during the conduct of the study; and, outside of the submitted work, grants and personal fees from Otsuka Pharmaceutical, non-financial support from Sanofi, and other support from the WHO.

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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 *et al*.[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

*The American Thoracic Society,[108] National Institute of Health and Care Excellence, UK[91] and World Health Organization[5] all have their own recommendations on this topic. The American Thoracic Society has recently updated their guidance on the treatment of drug sensitive disease, but at the time of writing new guidelines for treating drug resistant disease have not been released. INH- isoniazid, LTBI- latent tuberculosis infection, MDR- multidrug resistance

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	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] 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.	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

FIGURE LEGENDS

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

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

FIGURES

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