

Title: Treatment of Latent Tuberculosis: A Network Meta-Analysis - Update

Running title: Network meta-analysis of LTBI treatments.

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Financial support: 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.

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Word count: 2,627

Abstract

Background: Treatment of latent tuberculosis infection (LTBI) is an important component of tuberculosis (TB) control and this study updates our previous (network) meta-analysis on the best LTBI treatment options to inform public health action and the programmatic management of LTBI.

Purpose: To evaluate the comparative efficacy and harms of LTBI treatment regimens aimed at preventing active TB among adults and children.

Data sources: PubMed, Embase, Web of Science to 8th of May 2017; clinical trial registries; conference abstracts, including previous searches to 29th January 2014 and new searches since. No language restrictions.

Study selection: Randomized controlled trials that evaluated human LTBI treatment and recorded at least one of two pre-specified endpoints (preventing active TB, hepatotoxicity).

Data extraction: Data from eligible studies were independently extracted and study quality assessed by two investigators, according to a standard protocol.

Data synthesis: The network meta-analysis of new and previously included studies showed that isoniazid regimens of six or 12-72 months (odds ratio [OR] 0.31 [95% credible interval; CrI] 0.21- 0.47) , rifampicin only regimens OR 0.25 (CrI 0.11-0.57) , rifampicin-isoniazid regimens of three to four months OR 0.57 (CrI 0.31-1.02) , rifampicin-isoniazid-pyrazinamide OR 0.21 (CrI 0.11-0.41), and rifampicin-pyrazinamide OR 0.33 (CrI 0.18-0.58) regimens were efficacious compared with no treatment. There was evidence for efficacy of weekly rifapentine-isoniazid regimens OR 0.36 (CrI 0.18-0.73). There was no conclusive evidence that HIV status altered treatment efficacy.

Limitations: Sparse evidence for many comparisons and for hepatotoxicity outcomes was available and high or unknown risk of bias for many studies.

Conclusions: We found evidence for the efficacy and safety of six month isoniazid monotherapy and for rifampicin monotherapy as well as combination therapies with three to four months of isoniazid and rifampicin..

Registration: CRD42016037871 (PROSPERO).

Background

Tuberculosis (TB) is a global priority infectious disease with an estimated 1.4 million deaths in 2015 (1). A number of strategies are required if the Sustainable Development Goal of ending the global TB epidemic by 2030 is to be reached (2); tackling latent TB infection (LTBI) including providing preventive treatment to persons at high risk of TB, is a key action to achieve both the Sustainable Development Goals and the targets of the World Health Organization's End TB strategy(3).

A number of different treatment regimens for LTBI are currently available globally; five are recommended by the World Health Organization (4) and four of these by the Centers for Disease Control and Prevention (United States)(5). Evidence on efficacy of shorter regimens with a reduced pill burden is evolving, but more information on effectiveness is still urgently needed(6).

We previously published a network meta-analysis review of randomized controlled trials (RCTs) that identified the most effective and least harmful preventive treatment regimens (7). The results of this meta-analysis and Bayesian network analysis served as the evidence base for the 2014 World Health Organization's LTBI guidelines (4,8). As part of the European Centre for Disease Prevention and Control (ECDC)'s decision to provide new guidance on programmatic LTBI control in the European Union (EU)/ European Economic Area (EEA) and candidate countries, a need to update our 2014 review was identified (9) - the results of which are presented in this manuscript.

Methods

To ensure consistency, we used the same methodology as in our previous study (7). We

summarise this approach briefly below. We registered this study in the PROSPERO database (CRD42016037871).

Data sources and searches

PubMed, EMBASE, Web of Science and grey literature were searched until 8 May 2017. We reviewed and included our previous search and added all relevant articles, focussing on the time after the previous search (Annex 1).

Study selection and extraction

We followed the same selection criteria as before and included RCTs that analysed LTBI treatments, with no language restrictions. Exclusion criteria were non-randomised or observational studies, animal studies, or those, which did not have sufficient information on at least one of our two main end points (hepatotoxicity or development of active TB). As in our previous study, two of five potential reviewers (DZ, NB, HRS, MCL, MvdW) independently performed title, abstract, and full text screening, and resolved discrepancies through consensus or, if needed, through consultation with a third reviewer.

Data extraction and quality assessment

Two reviewers (DZ, NB) independently performed data extraction to a standardised template, which included details about the study, population and follow up, treatment regimens, and data on outcomes of interest. Study quality was assessed by the same two reviewers using the quality assessment tool from Higgins et al. (10). Disagreements were resolved in consultation with a third reviewer (MvdW).

Data synthesis and analysis

We compared both of the main outcomes – TB events and hepatotoxicity - using both conventional random effects meta-analysis and a network meta-analysis (NMA) approach. Analyses included grouping and stratification of treatment regimens and estimating differences in treatment effects between groups, via ratios of odds ratios (ROR), according to study-level variables as described in Stagg et al. (Data Supplement 1) (7). Pre-defined stratified analyses required studies to be grouped by (a) HIV status (HIV positive population versus not HIV positive population including low proportion HIV positive [$\leq 5\%$, including no individuals HIV positive] and not stated), (b) age (adults vs. children (<18)), (c) immunosuppressed (as a result of HIV infection and other conditions) versus not, (d) TB incidence in the country of study at the time of the RCT (high versus low incidence). The robustness of the HIV stratification was also tested by sensitivity analysis using a stricter definition of non-HIV status (non-HIV group only including studies where being HIV positive was an exclusion criterion and pre-1990 publications when endemic levels were low) (11).

Analyses of study and review quality were also undertaken as previously. The effect of study quality domains such as inadequate/unclear blinding, allocation concealment and randomisation, incomplete outcome assessment etc. were also assessed by estimating RORs between studies with adequate vs. inadequate/unclear study domains to determine whether these were associated with a change in estimated treatment efficacy. Publication bias was assessed in a similar way, to determine whether average standard errors (SE) of log odds ratios for each study were associated with a difference in estimated treatment efficacy. Network consistency was examined by informally comparing estimated treatment effects from NMA with standard pair-wise meta-analysis and comparing deviance information criteria (DIC) statistics for the NMA with an inconsistency model, in which the difference

between each possible comparison is unconstrained, rather than the usual NMA assumption of consistent treatment effects for different comparisons.

We used STATA 13 (Statacorp, Texas) for data processing and classical analysis, with the Bayesian NMA conducted using WinBUGS 1.4.3 (Medical Research Council, UK). Most figures were also produced with STATA, except flow charts for which Microsoft PowerPoint for Mac (Microsoft Corp) was used.

Role of Funding Source

Funding sources are outlined above. None of the funding sources had any influence or role in this review.

Results

In the update of the review, 1576 articles were identified in the databases search and of these, 1434 were left after de-duplication (Data Supplement 2). Eight additional papers were selected that were either used to update or to add to the 53 studies included in the original review (Data Supplement 3). Two of the added papers provided data from studies that had been included in the original review (12,13). Samandari (2015) (12) overlapped with Samandari (2011) (14); the former was used to provide an update for the outcome of development to active TB, but did not report any additional hepatotoxicity results. Sterling (2016) (13) provided an update solely for the people living with HIV included in their original 2011 paper (15). In the interest of analytical power we thus retained Sterling (2011) for the overall analysis, but utilised Sterling (2016) (13) when performing the HIV stratified analysis. In Danel (16), there were four arms, two comparing patients with deferred antiretroviral therapy (ART) and two comparing patients with early ART initiation. Data were extracted and analysed separately for both groups of patients.

Four of the new papers contained extractable data on hepatotoxicity (12,16–18) and all eight on development of active TB (12,13,16–21). Six of the eight papers were conducted in TB high incidence countries (12,16,17,19–21) and six were solely in people living with HIV (12,13,16–19). All new studies included isoniazid (INH) monotherapy in at least one arm; additionally, one included INH-rifapentine (RPT)(13), one included INH-ethambutol (EMB)(21) and one included both INH-rifampicin (RMP) and INH-pyrazinamide (PZA)(18) (Data Supplement 4). Sixteen regimens were thus included in the evidence network, one more (INH-EMB 12 months) than in the previous review (Table 1, Figure 1 and 2)

Study quality

A number of the newly included papers had a high or unknown risk of bias (Data Supplement 7). As previously, however, all study quality indicators for high risk of bias were only associated with very weak evidence for modification of treatment efficacy; for instance inadequate/unclear allocation concealment had a ratio of odds ratios (ROR) of 0.74 (95% credible interval [CrI] 0.31-1.42). Similar results were observed for high or unclear risk of bias due to inadequate randomisation and blinding, which is consistent with other studies (22). The ROR for incomplete/unclear outcome reporting versus adequate was 0.91 (95% CrI 0.42-1.43) and for selective reporting 1.03 (95% CrI 0.55-1.75).

Results for hepatotoxicity were highly uncertain for all domains due to the sparsity of data and there was no firm evidence with which to confirm or reject any modification of treatment effects according to study quality domains.

Prevention of active TB

An assessment of sixteen different regimens found that INH regimens of six or 12-72 months, RMP only regimens, RMP-INH regimens of three to four months, RMP-INH-PZA, RMP-

PZA, and INH-EMB 12 month regimens were efficacious, with p-values <0.05. Table 1 shows estimated odds ratios (ORs) for each regimen vs. placebo and no treatment under the NMA model. The INH-EMB 12 month regimen showed the greatest effect, but with substantial uncertainty (OR=0.20, 95% CrI: 0.04, 0.82) and INH-EMB for shorter durations showed no evidence of efficacy. Two RFB-INH regimens, which used different doses of RFB, both showed ORs of 0.30 but with substantial uncertainty. The RMP-INH-PZA combination regimen showed a two-thirds reduction in TB and was strongly significant (OR=0.35, 95% CrI: 0.19, 0.61). Additionally, the use of (three or four months of) RMP and three or four months of RMP-INH appeared to be efficacious, with reductions in active TB of a half or more, although these results are based on limited data. The ORs for all lengths of INH had overlapping CrIs and varying levels of uncertainty, with INH regimens of 6 or 12 months or more having the most robust evidence and the with greatest efficacy for 12 months or more. Treatment rankings, while not providing quantified differences of treatment efficacy, are also useful in understanding uncertainty in the evidence base. For instance, the INH-EMB 12 month regimen had the highest median rank, but credible intervals also included it being ranked among the poorest (95% CrI 1st-11th); the INH regimen of 12 months or more had more certainty but was ruled out of being one of the best, and a number of other regimens had 95% CrIs that included being the best-ranking treatment (RFB-INH regimens, RMP and RMP-INH-PZA). Treatment rankings are shown in Table 1 and histograms of rankings are available in Data Supplement 8 and 9.

Stratifying the results on the basis of HIV status showed no significant differences in effect estimates for each regimen or the overall pattern of results when comparing studies in exclusively HIV positive populations (24 studies) versus those without HIV or where this was not stated (28 studies; Data Supplement 9). The estimated ROR for the overall difference

in treatment efficacy (1.45, 95% CrI 0.89-2.31) indicates an inconclusive but potentially weaker efficacy for treatment versus placebo/no treatment in HIV positive individuals. The standard deviation of the random effect for treatment modification was 0.164 (95% CrI 0.007-0.957), indicating reasonable consistency across regimens for differences in treatment efficacy, albeit with wide CrIs.

Inclusion of high versus low TB incidence in the country of study as a covariate reduced between-study variability; treatment was generally less efficacious in high incidence populations (ROR 1.58, 95% CrI 1.01-2.48). Subgroup analysis by year and age also resulted in little change in treatment rankings. Using covariate models, treatment effects were attenuated slightly in more recent years, although the evidence for this was fairly weak (ROR 1.58, 95% CrI 0.82-2.82 and 1.34, 95% Cr: 0.59-2.38 for 1992-2004 and 2005 onwards versus pre-1992, respectively). There was no evidence of a relationship between adherence and efficacy (ROR 0.94 per 10% decrease, 95% CrI 0.54-1.30). Restricting analysis to culture confirmed TB cases only did not alter our conclusions.

Comparing the results derived from a random effects pairwise meta-analysis with the corresponding estimate from the NMA model revealed some differences in OR estimates between the models (Figure 2, Data Supplement 5 and 10). Many treatment comparisons showed a stronger beneficial effect in a standard pairwise meta-analysis compared to results from NMA; however the differences had p-values greater than 0.05 and were predominantly where the effect estimates from pairwise meta-analysis were imprecise.

Hepatotoxicity

Due to the limited data on hepatotoxicity, results from the direct comparison are presented

here. Hepatotoxicity results from the NMA are shown in Table 2. Estimates were largely consistent with the direct comparisons (Data Supplement 7, 9 and 11). Twenty different pairwise comparisons were available. Results from the standard meta-analysis suggest that RMP only and RPT-INH regimens had lower rates of hepatotoxicity than an INH only regimen of six, nine, or 12-72 months (Data Supplement 6 and 10). RMP-INH regimens also had lower hepatotoxicity versus INH only regimen, although there was only good evidence for this when compared to INH regimens of 12-72 months. There was good evidence that regimens containing PZA had higher hepatotoxicity compared to six months of INH or 12 weeks of RPT-INH. No data were available regarding the hepatotoxicity of the RFB-INH and INH-EMB regimens. Stratifying the results on the basis of immunosuppression, HIV status and TB incidence did not markedly impact on our conclusions.

Inconsistency

Comparing inconsistency models with the consistency models revealed no evidence that the additional complexity of the former was required (Data Supplement 12). However, as this study used a full random effects model and the data exhibited a moderate level of between-study heterogeneity, the power to detect inconsistency was low and this result cannot be interpreted as conclusive evidence of the consistency of the network. Results from four studies, including Ma Lin (21), were extreme in comparison with other studies, but these data points fitted poorly in both the NMA and the inconsistency model, indicating extreme heterogeneity rather than non-transitivity.

Publication bias

In pairwise meta-analysis there was no evidence for the exaggeration of treatment effects in smaller studies (a proxy for publication bias) in any of the comparisons (minimum p-

value=0.300, Harbord test). In NMA the covariate effect for study SE indicated that estimated treatment effects tended to show a greater benefit in smaller, less precise studies, although this result was not significant (ROR per 0.2 change in SE: 0.83, 95% CrI 0.66-1.04) (Data Supplement 13).

Discussion

We present the results of an updated review and meta-analysis investigating the efficacy and toxicity of treatment regimens for LTBI (7). This review confirms that all currently recommended regimens (4) are safe and efficacious and provides more robust evidence to demonstrate the efficacy of rifamycin-containing regimens, including the three to four months RMP monotherapy, to prevent TB disease. Whilst we also included a new study on the efficacy for ETH-INH combination therapy, both INH and INH-ETH combination had zero TB cases in this small study, and the study therefore did not significantly add to the evidence of the network. There were no significant differences in treatment efficacy for the different regimens in HIV positive and HIV negative subjects, although there was a possible general weakening of efficacy in HIV positive populations. Studies in HIV positive populations have only been conducted relatively recently and are therefore highly correlated with year of publication; more recent studies were also associated with a modest decrease in treatment efficacy, so there may be some confounding.

Aside from the efficacy of a particular regimen and its toxicity and risk of adverse events, in clinical practice three other key factors should be considered when making recommendations. These are the cost of a regimen, the length of time for which patients are taking treatment and pill burden. A recent systematic review showed that shorter regimens were associated with higher treatment completion rates (23). The relatively brief three-month RPT-based regimen

has obvious advantages in terms of shortened treatment length, with only 12 doses. Publications from a general population setting (15), amongst HIV infected persons (13), or children and adolescents (24) have demonstrated good efficacy and safety. Unfortunately, as these publications derive from the same core study, the evidence as demonstrated within our network remains limited.

Only few other systematic reviews on the topic have been published recently. Our search revealed two papers, where LTBI treatment efficacy and toxicity has been part of a wider review (25,26) and a further three which focussed on specific populations, two on children (27,28) and one on HIV-infected adults (29). The nature of these reviews means that their study collection tends to be more restricted than ours, but the results are compatible with ours in all studies.

Our search also revealed two ongoing registered trials. One of these (NCT02651259), which aims to evaluate the pharmacokinetics, acceptability and safety of the rifapentine-isoniazid regimen in pregnant and post-partum women is currently recruiting participants and is expected to complete recruitment in December 2018 (30). The other (NCT02980016) is a pragmatic trial which looks at incidence and treatment completion rates among an HIV positive population, comparing a single rifapentine-isoniazid course with a six month isoniazid regimen and in a second stage with a periodic rifapentine-isoniazid regimen (31). This trial is also in recruitment phase, scheduled to complete in June 2019. Both trials look at important aspects of rifapentine-based regimens and support the much-needed development of shorter and less frequent LTBI treatment regimens.

Our study presents two parallel forms of meta-analysis. Effect estimates can sometimes show

greater benefit in pairwise comparisons compared to NMA, with the latter constraining treatment effects to be consistent across comparisons. Although not significantly different, it is possible that treatment effects reported in our pairwise results could be slightly overestimated.

The main limitation of our work is the underlying studies, many of which have a high risk of bias and are small or use non-standard endpoint definitions. A number of publications reported on overlapping RCT populations; we carefully avoided double counting by applying standard inclusion rules to these studies. In general this meant including the study with the largest cohort and greatest follow up time, which was often the most recent work. Since the highest LTBI reactivation risk usually occurs shortly after infection, prolonging cohort follow-up time may lead to decreased effect estimates, particularly for long-term regimens. Our replacement of efficacy estimates from Samandari (2011)(14) with those from their 2015 paper demonstrated this; the efficacy of 36 months INH treatment waned over time. It is possible, therefore, that our analysis provides conservative efficacy estimates in some instances particularly for longer regimens – in particular in high TB burden settings where there is much greater potential for reinfection. We tested for publication bias, however, our ability to do so was limited for some comparisons, due to sparse data. Lastly, whilst we provide stratified analyses for a number of co-variables, including HIV co-infection, there is a dearth of evidence on how concomitantly administered treatments such as HIV anti-retrovirals (ART) may interact with LTBI treatment efficacy. Although there have been some recent insights (32), demonstrating an LTBI treatment-independent effect of early ART start on TB incidence (16), data points were too limited to include ART as a co-factor in our analysis.

In conclusion, despite limitations in underlying evidence including study quality and varying reporting standards, the evidence for safety and efficacy of most standard treatment regimens is robust, although there remains sparse evidence for the 9 month INH regimen. The evidence for rifamycin containing regimens including RPT is improving. More evidence is needed, particularly for RPT-based regimens and the INH-RMP combination, alternative treatments with shorter duration and lower pill burden, and to assess the impact of co-variates such as ART. It is reassuring nonetheless to reaffirm the strengthening evidence for shorter rifamycin regimens.

Acknowledgments:

ML would like to acknowledge the UK National Institute of Health Research for 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.

We would like to thank Siyue Zhang and Dr Hongxin Zhao for assisting us with the Chinese translation.

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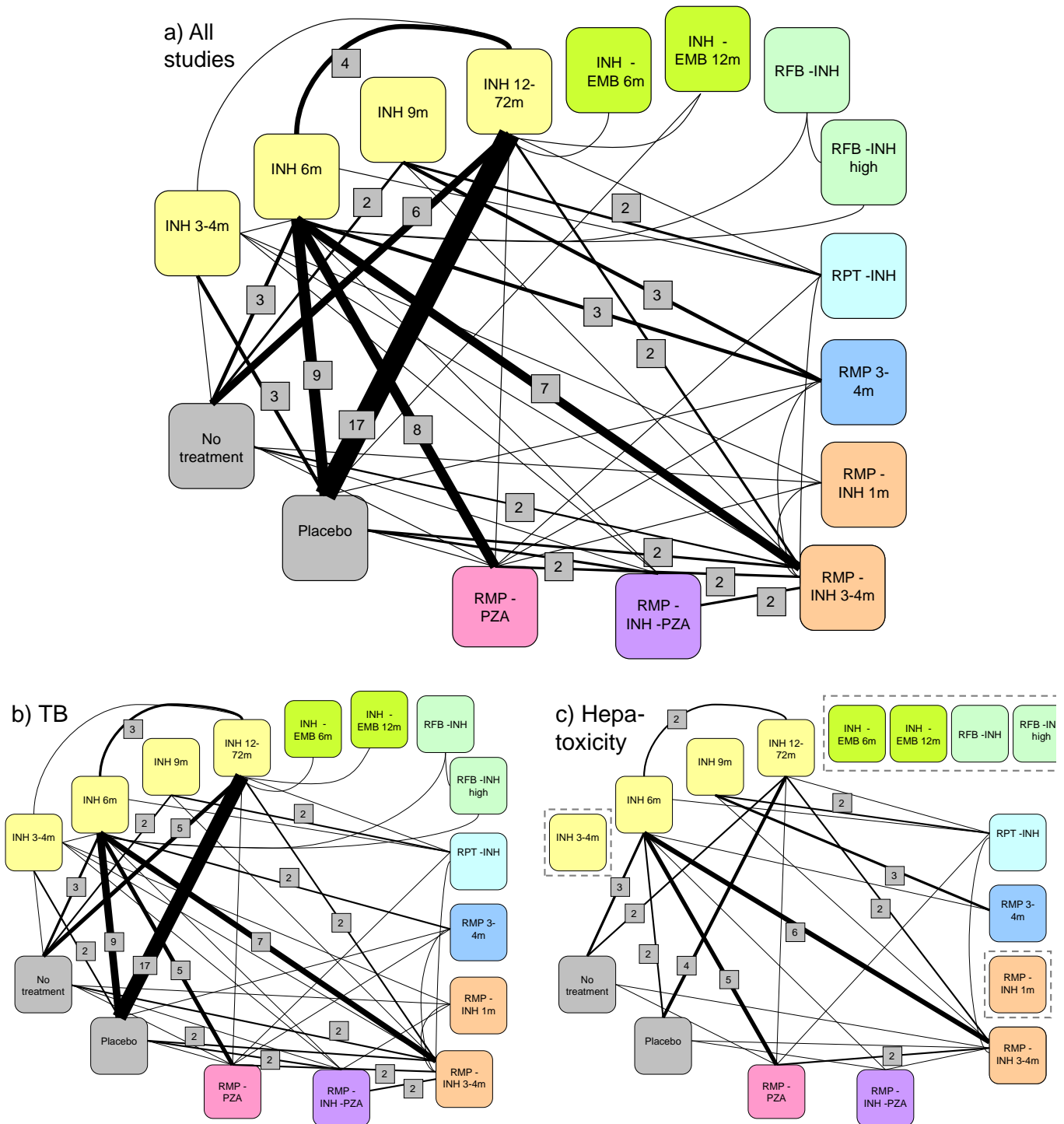
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Figure 1: Treatment network for a) all studies, b) those with active tuberculosis data and c) those with hepatotoxicity data*



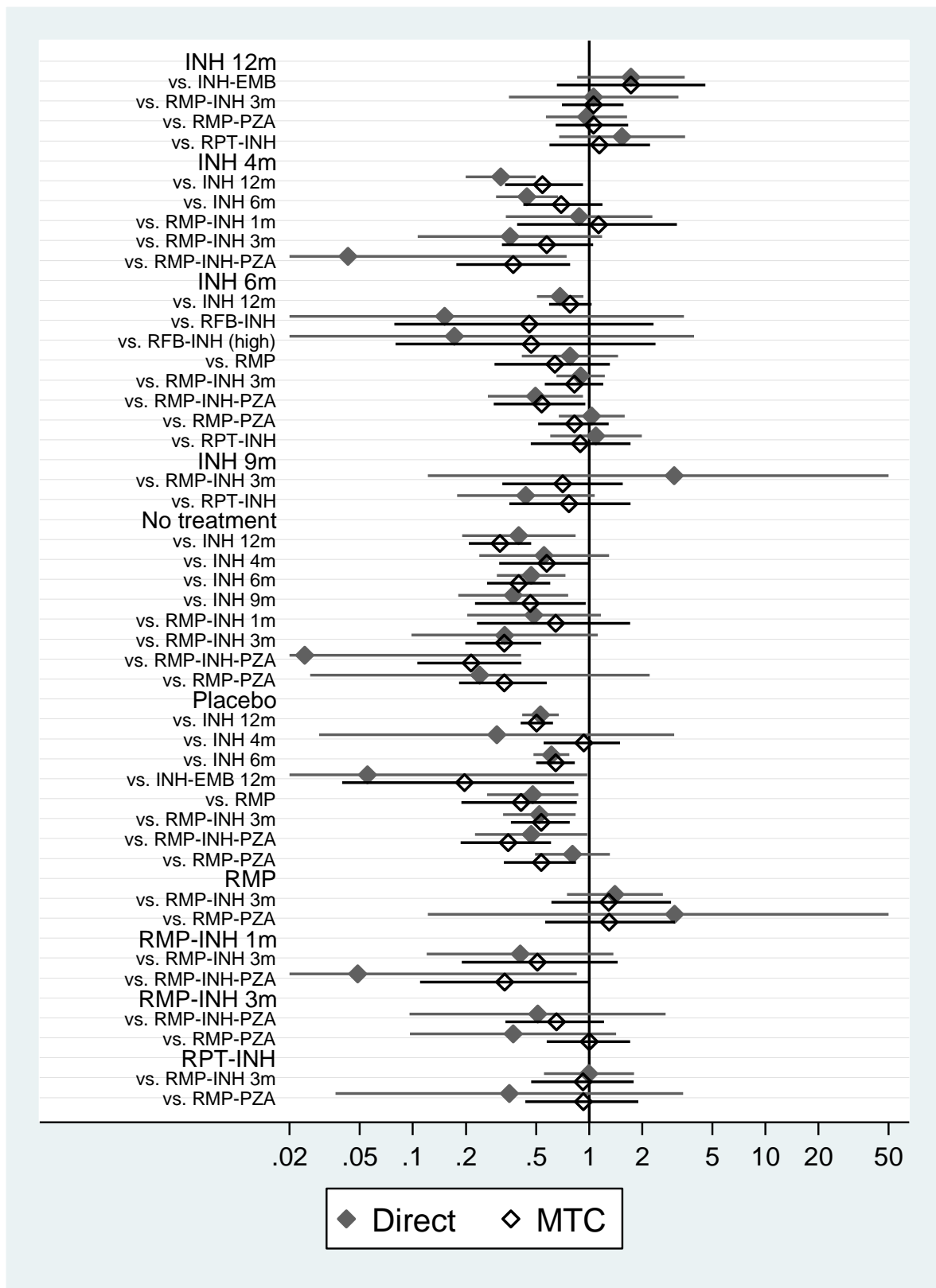
* Unlabelled connections indicate one study reporting that treatment pair; for two or more studies lines are proportionally thicker, and labelled with the number of studies. Colour coding indicates classes of treatment. Dotted boxes indicate a lack of data. RFB-INH: 300mg RFB plus 750mg INH twice weekly for 3 months, RFB-INH high: 600mg RFB plus 750mg INH twice weekly for 3 months. 4m- four months, etc., EMB- ethambutol; NH- isoniazid; PZA- pyrazinamide; RFB- rifabutin; RMP- rifampicin; RPT- rifapentine; TB- tuberculosis

Table 1: Odds ratios for the prevention of active tuberculosis and treatment rankings, derived from the network meta-analysis*

Regimen	OR vs. placebo (95% CrI)	OR vs. no treatment (95% CrI)	Rank (95% CrI)
No treatment	1.62 (1.06, 2.47)	1 (ref)	16 (14-16)
Placebo	1 (ref)	0.62 (0.41, 0.94)	13 (11-15)
INH 3-4m	0.93 (0.55, 1.50)	0.57 (0.31, 1.02)	13 (8-15)
INH 6m	0.65 (0.50, 0.83)	0.40 (0.26, 0.60)	10 (7-12)
INH 9m	0.75 (0.35, 1.62)	0.46 (0.22, 0.95)	11 (4-15)
INH 12m	0.50 (0.41, 0.62)	0.31 (0.21, 0.47)	6 (4-10)
RFB-INH	0.30 (0.05, 1.50)	0.18 (0.03, 0.95)	3 (1-15)
RFB-INH (high)	0.30 (0.05, 1.52)	0.19 (0.03, 0.98)	3 (1-15)
RPT-INH	0.58 (0.30, 1.12)	0.36 (0.18, 0.73)	8 (3-14)
RMP	0.41 (0.19, 0.85)	0.25 (0.11, 0.57)	5 (1-12)
RMP-INH 1m	1.05 (0.37, 2.77)	0.65 (0.23, 1.71)	14 (4-16)
RMP-INH 3-4m	0.53 (0.36, 0.78)	0.33 (0.20, 0.54)	7 (4-11)
RMP-INH-PZA	0.35 (0.19, 0.61)	0.21 (0.11, 0.41)	3 (1-8)
RMP-PZA	0.53 (0.33, 0.84)	0.33 (0.18, 0.58)	7 (3-12)
INH-EMB	0.87 (0.32, 2.36)	0.54 (0.19, 1.56)	12 (4-16)
INH-EMB 12m	0.20 (0.04, 0.82)	0.12 (0.02, 0.54)	2 (1-11)

* Comparisons versus placebo and no treatment. CrI- credible interval, EMB- ethambutol, INH- isoniazid, m- months, OR- odds ratio, PZA- pyrazinamide, RFB- rifabutin, RMP- rifampicin, RPT- rifapentine

Figure 2: Comparison of odds ratios for active tuberculosis obtained from random effects pairwise meta-analysis with corresponding estimate from mixed treatment comparison (NMA)†



† Where data on direct comparisons of treatment pairs are available for active tuberculosis these may be pooled via standard meta-analysis for each pair of treatments in turn. The resulting estimates are then compared with those obtained from the NMA analysis, which incorporates indirect evidence and the overall network structure in addition to the direct evidence. EMB- ethambutol, INH- isoniazid, m- months, PZA- pyrazinamide, RFB- rifabutin, RMP- rifampicin, RPT- rifapentine

Table 2. Odds Ratio for Hepatotoxicity, derived from the Network Meta-analysis

Regimen	OR vs. no treatment (95% CrI)	OR vs. placebo (95% CrI)	Rank (95% CrI)
No treatment	1.00 (1.00, 1.00)	0.24 (0.06, 0.75)	4 (2-7)
Placebo	4.12 (1.33, 15.88)	1.00 (1.00, 1.00)	9 (7-10)
INH 6m	1.10 (0.40, 3.17)	0.27 (0.10, 0.60)	5 (3-7)
INH 9m	1.70 (0.35, 8.05)	0.41 (0.08, 1.62)	6 (3-10)
INH 12m	2.72 (0.96, 7.44)	0.66 (0.26, 1.32)	8 (6-10)
RPT-INH	0.52 (0.13, 2.15)	0.13 (0.03, 0.42)	2 (1-5)
RMP	0.14 (0.02, 0.81)	0.03 (<0.02, 0.16)	1 (1-2)
RMP-INH 3-4m	0.72 (0.21, 2.37)	0.17 (0.05, 0.46)	3 (2-6)
RMP-INH-PZA	2.41 (0.25, 20.02)	0.58 (0.07, 3.72)	7 (2-10)
RMP-PZA	3.32 (0.99, 11.23)	0.80 (0.25, 2.17)	9 (6-10)

CrI- credible interval; INH- isoniazid; PZA- pyrazinamide; RMP- rifampicin; RPT- rifapentine

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