

## Systematic Review and Meta-Analysis of Isoniazid Pharmacokinetics Among Healthy Volunteers and Patients with Tuberculosis

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### ABSTRACT

**Purpose:** To derive and compare isoniazid (INH) pharmacokinetic (PK) summary estimates between healthy volunteers and TB patients, evaluate whether the current INH dose regimen is appropriate in TB patients, and evaluate the impact of N-acetyl-transferase-2 (NAT2) status on INH PK.

**Methods:** A systematic approach was conducted to find studies with relevant INH PK data published in the English language up to February 2018. INH PK parameters were extracted with their respective INH dosages and were dose-normalized to allow a fair comparison between healthy volunteers and TB patients. Meta-analysis was then performed for the  $C_{max}$  and AUC estimates for all INH dosages

**Findings:** Ninety studies were included in this systematic review. TB status significantly affected the INH  $C_{max}$  and AUC estimates. In adult healthy volunteers, the dose-normalized INH  $C_{max}$  and AUC were statistically higher than TB patients. There were no significant differences in dose-normalized  $C_{max}$  and AUC between TB and TB/HIV patients in adults; however, pediatric AUC was significantly different between TB and TB/HIV patients. Additionally, no significance was observed comparing the dose-normalized  $C_{max}$  and AUC of pediatric TB and TB/HIV patients to their respective adult counterparts. Dose-normalized INH  $C_{max}$  and AUC in fast and intermediate NAT2 patients were significantly lower than slow NAT2 patients.

**Implications:** The current recommended dosages of INH were found to produce less drug exposure in TB patients when compared to healthy volunteers. NAT2 polymorphism greatly impacts INH PK, hence testing for acetylator status is highly recommended and therapeutic drug monitoring would help reduce INH toxicity.

**Keywords:** Isoniazid; Pharmacokinetics; Meta-analysis; Systemic Review; TB patients

## 1 Introduction

2 Isoniazid (INH) has been a key drug for treating drug-susceptible TB for decades. When combined with  
3 other first-line medications, including rifampicin (RIF), ethambutol (EMB), and pyrazinamide (PZA),  
4 treatment duration is manageable and usually effective. As of 2017, there were 558,000 TB drug-resistant  
5 cases estimated worldwide—where 82% of these cases were considered MDR-TB showing resistance to  
6 both INH and rifampicin [1]. As a result, the need for an adequate TB treatment is imperative.

7  
8 Despite the wide use of INH, the optimal dose to treat TB has not been established. The drug was  
9 discovered in 1952, thereafter INH has been combined with other anti-tuberculosis agents to combat TB  
10 and drug resistance [2]. However, differences in PK between healthy volunteers and TB or TB/HIV  
11 coinfecting patients are not well-known. Patients with diabetes, HIV, and other gastrointestinal problems  
12 are at risk for poor drug absorption. Further, drug-food or drug-drug interactions also might affect INH  
13 absorption, and in turn may lead to poor treatment outcomes.

14  
15 In terms of therapeutic drug monitoring (TDM), AUC is an indicator of clinical outcomes in TB patients,  
16 in which an AUC of  $\leq 52$  mg·hr/L was shown to be associated with a poor outcome [3]. An INH  $C_{\max}$  of 3-  
17 6 mg/L from daily INH 300 mg dose and 9-15 mg/L from 900 mg bi-weekly dose is desirable; however,  
18 plasma concentrations alone cannot guarantee TB treatment outcome [4].

19  
20 INH absorption is greatly hindered by the presence of food in the stomach [5], and it is extensively  
21 metabolized by the liver where it undergoes phase II conjugation via N-acetyltransferase-2 (NAT2).  
22 Studies have shown NAT2 polymorphism affects the plasma concentrations of INH [6-8]. Adult patients  
23 who are fast acetylators may have suboptimal exposures with the current INH dose of 5 mg/kg [9]. Patients  
24 with slow NAT2 may display higher AUCs and thus may have significantly greater bactericidal activity  
25 than intermediate and fast NAT2 patients [10]. Therefore, the relationship between NAT2 and INH PK

26 requires further examination. In terms of safety, the risk of hepatotoxicity may be increased in patients who  
27 are slow metabolizers [11-14].

28

29 The currently available INH PK data in literature are from relatively small cohorts and more robust data is  
30 needed. Additionally, there are inconsistencies in INH concentrations for TB patients. For these reasons, a  
31 systematic review and meta-analysis was conducted in order to obtain and summarize INH  $C_{max}$  and AUC  
32 data. The objectives of this study were: (i) to derive and compare INH PK summary estimates between  
33 healthy volunteers and TB patients; (ii) to evaluate whether the current INH dose regimen is appropriate in  
34 TB adult and pediatric patients; and (iii) to evaluate the effect of NAT2 status on INH  $C_{max}$  and AUC.

35

## 36 **Methods**

### 37 **Search Strategy and Selection Criteria**

38 A systematic literature search was conducted following the Preferred Reporting Items for Systematic  
39 Reviews and Meta-Analyses (PRISMA) guidelines [15]. The electronic databases used were: PubMed,  
40 EMBASE, and Scopus. Studies were identified using the search terms: ((INH OR isoniazid OR  
41 antimycobacterial) AND pharmacokinetics AND antituberculosis). The search was conducted for the  
42 period from the earliest study in 1966 to February 2018 in English. R. D. and B. L. H. assessed titles and  
43 abstracts for relevance and reviewed full texts for inclusion with regards to the selection criteria. Studies  
44 were included if they reported INH PK data from healthy adult volunteers or from patients with TB.  
45 Patients who received INH for indications other than TB, specifically other mycobacterial infections, were  
46 excluded. In vitro studies, studies without INH  $C_{max}$  and AUC, and studies that assessed PK under fed-state  
47 (when indicated), were excluded. Furthermore, reviews or systematic reviews of INH PK were also  
48 excluded to avoid potential data duplications.

49

## 50 **Quality of Studies Assessment**

51 There are no validated tools to evaluate PK studies. However, our priority was to obtain studies that  
52 represented the target population which received INH and reported relevant PK parameters. All INH dose  
53 ranges were considered in this analysis. In order to enhance the data extraction process, we only included  
54 the articles in which authors precisely described their study sample, pharmaceutical product, method, and  
55 statistical tools for analysis.

56

## 57 **Data Extraction**

58 A standardized extraction form was developed by R. D. and was later modified by B. L. H. Two reviewers  
59 (P. L. and B. L. H.) extracted data from the included studies. The parameters of interest included study  
60 population and size, age (adult  $\geq 18$  years old, pediatric  $< 18$  years old), gender, body weight, INH  $C_{max}$   
61 and AUC, formulation and route, treatment frequency and duration, NAT2 status, TB status, HIV status,  
62 smoking status, malnourishment, and analytical method. In addition, subjects in studies must be in a  
63 fasting-state prior to taking INH.

64

## 65 **Data Synthesis**

66 In many studies, multiple groups of subjects were compared [16]. In others, crossover studies were  
67 performed in order to compare different INH formulations [17]. These groups were handled as separate  
68 study arms as presented in the study; each contributed their own set of INH PK data towards the summary  
69 estimates instead of a composite mean value for each study. Therefore, some studies contributed more than  
70 one set of PK parameters towards this meta-analysis. The forest plots were handled using the same process.  
71 Subjects in studies without any reported INH PK data were excluded, as a result, only subjects with INH  
72 PK data were included in this meta-analysis. To enable a comparison between all studies, sample size, data  
73 means and standard deviations (SD) were collected for the meta-analysis.

74

75 When studies did not include body weight of adult subjects, we used the world average body weight of 62-  
76 kg to calculate body-weight dosing (mg/kg) [18]. Body-weight dosing was used to dose-normalize INH PK  
77 data for a fair comparison across all doses. Additionally, the majority of healthy adult volunteers only took  
78 INH; whereas TB patients commonly took INH in combination with other anti-tuberculosis medications  
79 (i.e. RIF, EMB, and PZA). Therefore, subjects were included if they took INH alone or in combination  
80 with other antituberculosis medications. Any subjects taking INH with other co-medications were also  
81 included if the study concluded that the co-medications did not significantly impact INH PK.

82

83 The majority of INH studies have reported  $C_{\max}$  and AUC data in mean $\pm$ SD, but there were others that only  
84 reported the mean or median and omitted standard deviation. This was especially true in the earlier INH  
85 studies; therefore, we formulated various assumptions and methods to estimate and reconcile the  
86 differences in these study data. If raw data were available in studies, we used that to calculate the mean and  
87 standard deviation for those studies. If the AUC was not explicitly stated in the study while raw data were  
88 available, we performed non-compartmental analysis (NCA) on the plasma concentrations over time (four  
89 blood-sample collection time minimal) to estimate the AUC. The AUC of studies were excluded if the  
90 duration of sample collection was less than six hours, since the full drug-plasma level is difficult to  
91 estimate accurately with less than three half-lives of collection (less than six hours). Since studies reported  
92 a mixture of single-dose and steady-state AUC, along with different AUC range (i.e.  $AUC_{0-6h}$ ,  $AUC_{0-8h}$ ,  
93  $AUC_{0-12h}$ , etc.) in tables, this would make it difficult to compare and summarize the data for the analysis.  
94 Subsequently,  $AUC_{0-6h}$  or greater was considered as representing AUC and the combination of single-dose  
95 and steady-state AUC were combined in this analysis. If data were given in median, range, or IQR, these  
96 were standardized to mean and standard deviation via the described method [19].

97

98 **Summary Measures**

99 The data were gathered on a standard extraction form. The focus of this study was to collect INH  $C_{\max}$  and  
100 AUC across various doses from all subjects who received INH. A linear model was used to include these  
101 variables: healthy adult vs TB adult/pediatric patients, HIV status, and NAT2 status (fast, intermediate, or  
102 slow). Data were dose-normalized to prepare for entry and were analyzed by Open Meta-Analyst  
103 (<http://www.cebm.brown.edu/openmeta/>) software using the random-effects/DerSimonian-Lard method to  
104 generate forest-plots and summary mean estimates of INH  $C_{\max}$  and AUC, and calculate heterogeneity ( $I^2$ )  
105 [20]. Finally, the p-value was obtained using unpaired, two-tailed Student's t-tests performed in Excel, in  
106 which 0.05 or less were considered statistically significant. The degree to which INH dose impacted  $C_{\max}$   
107 and AUC was assessed using meta-regression by Open Meta-Analyst.

108

## 109 **Results**

110 The systematic literature search retrieved 4,911 studies, of which 90 studies met the INH inclusion criteria  
111 (Figure 1) and a brief summary of these studies is outlined in Table S1 (available as Supplementary Data).  
112 The health, age, and NAT2 status of study participants, and the number of PK sets contributed by  
113 participants are presented in Table 1-3. The majority of studies used HPLC to measure INH concentrations.  
114 The results for  $C_{\max}$  and AUC presented henceforth include all dose ranges of INH reported in the studies.  
115 Unless explicitly stated, any  $C_{\max}$  and AUC mentioned hereafter will refer to the dose-normalized  $C_{\max}$  and  
116 AUC measures.

117

118 TB status significantly affected the  $C_{\max}$  and AUC estimates of INH. In healthy volunteers, the dose-  
119 normalized INH  $C_{\max}$  and AUC were statistically higher than TB adult, with  $P < 0.0001$  for  $C_{\max}$  and  $P =$   
120  $0.0006$  for AUC (Table 1 and Table 2). The same results were seen when comparing healthy adult  
121 volunteers to TB pediatric patients ( $P < 0.0001$  and  $P = 0.0002$  for  $C_{\max}$  and AUC, respectively). The same  
122 trends were also observed for dose-normalized  $C_{\max}$  and AUC when comparing healthy adult volunteers to  
123 TB/HIV adult and pediatric patients. Dose-normalized  $C_{\max}$  and AUC for healthy adult volunteers were

124 1.089 (mg/L)/(mg/kg) [95% CI, 0.969-1.209] and 4.329 (mg·hr/L)/(mg/kg) [95% CI, 3.818-4.840],  
125 respectively; whereas adult dose-normalized  $C_{max}$  and AUC for TB patient were 0.698(mg/L)/(mg/kg)  
126 [95% CI, 0.637-0.759] and 3.183 (mg·hr/L)/(mg/kg) [95% CI, 2.804-3.563], respectively. Similarly, dose-  
127 normalized  $C_{max}$  and AUC for pediatric TB patient were 0.618 (mg/L)/(mg/kg) [95% CI 0.517-0.718] and  
128 2.695 (mg·hr/L)/(mg/kg) [95% CI, 2.315-3.075]. The dose-normalized AUC forest plots of INH are shown  
129 in Figure S1 (available as Supplementary Data) and Figures 2-4. Despite dose-normalization for  $C_{max}$  and  
130 AUC, pooled statistics demonstrated that high heterogeneity was present throughout this meta-analysis ( $I^2$   
131  $> 88\%$ , with the only exception being INH AUC for pediatric TB/HIV,  $I^2 \sim 60\%$ , demonstrating moderate  
132 heterogeneity).

133

134 Dose-normalized  $C_{max}$  and AUC for pediatric TB only were not statistically significant when compared to  
135 their adult TB counterparts ( $P = 0.18$  and  $P = 0.16$ , respectively). There was also no difference perceived  
136 for pediatrics with TB/HIV and adults with TB/HIV when their  $C_{max}$  and AUC ( $P = 0.11$  and  $P = 0.22$ )  
137 measures were compared. However, there was a significant difference in AUC between pediatric TB  
138 patients and pediatric TB/HIV patients ( $P = 0.007$ ); this difference was not seen in  $C_{max}$  for these two  
139 groups ( $P = 0.34$ ).

140

141 Polymorphism of NAT2 impacted dose-normalized INH  $C_{max}$  and AUC. The effect was most apparent  
142 between slow NAT2 and intermediate/fast NAT2 subjects (Table 3). The dose-normalized  $C_{max}$  was  
143 significantly lower for intermediate ( $P = 0.017$ ) and fast ( $P < 0.0001$ ) NAT2 acetylators compared to slow  
144 NAT2 acetylators. Likewise, the AUC was significantly lower for intermediate ( $P < 0.0001$ ) and fast ( $P <$   
145  $0.0001$ ) NAT2 acetylators than slow NAT2 acetylators.

146

147 The  $C_{max}$  and AUC appeared to increase proportionally to INH dosage. Meta-regression shows a linear  
148 relationship between INH body-weight dosing and  $C_{max}$  and AUC (Figure 5).

149

150

**151 Discussion**

152 The dose-normalized summary estimates of  $C_{\max}$  from TB population is significantly lower than that of  
153 healthy volunteers (36% lower in TB adults, 39% lower in TB/HIV adults, 43% lower in TB pediatrics, and  
154 54% lower in TB/HIV pediatrics). This result of TB/HIV adult patients support what was observed in  
155 another study where  $C_{\max}$  of TB/HIV adult patients had INH concentrations below the reference range of 3-  
156 6 mg/L (54/77 patients at week-2, 38/59 patients at week-8, and 15/24 patients at week-24 were below the  
157 reference range) [21]. Likewise, the dose-normalized INH AUC from TB population was significantly  
158 lower than that of healthy volunteers (26% lower in TB adults, 42% lower in TB/HIV adults, 38% lower in  
159 TB pediatrics, and 61% lower in TB/HIV pediatrics). This great disparity in INH PK between healthy adult  
160 volunteers and TB patients demonstrate the necessity to adjust INH dose. Consequently, the current  
161 recommended INH dose regimen may not be sufficient in treating both TB adult and pediatric patients, and  
162 an increase in the INH dose may be needed.

163

164 In our analysis, many of the healthy adult volunteers took INH only, whereas TB patients took INH in  
165 combination with other antituberculosis drugs. This may have contributed to the observed difference in  
166  $C_{\max}$  and AUC between healthy adult volunteers and TB patients. However, the major pathway of INH  
167 metabolism is via NAT2 whereas RIF/EMB/PZA were eliminated through other pathways. Additionally,  
168 there are no known drug-drug interactions between INH and RIF/EMB/PZA that reduces INH  
169 concentrations [22]. Therefore, the impact of coadministration of other antituberculosis medications on  
170  $C_{\max}$  and AUC is likely negligible. Patients with TB/HIV may have some medications that may interact  
171 with antituberculosis drugs, but studies have found that the coadministration with efavirenz, tenofovir,  
172 emtricitabine, and nevirapine did not clinically affect the PK of INH [23, 24].

173

174 When the disposition of INH between pediatric and adult populations were compared, our meta-analysis  
175 showed that no difference was observed in INH PK between the TB adult patients and TB pediatric  
176 patients. This may indicate that TB does not impact INH PK due to age differences; therefore, this finding  
177 suggests that adult and pediatric INH dosing increase may be similar in magnitude if dose adjustment is  
178 warranted. When it comes to the revised WHO guideline for TB pediatrics, there is conflicting data about  
179 INH concentration. A study suggested that pediatric TB patients did not reach target range of INH  
180 concentration after taking INH 10 mg/kg body weight dosing [25]. On the contrary, another study  
181 suggested that a 10 mg/kg body weight dosing caused above normal range of  $C_{max}$  and AUC in pediatric  
182 TB patients, and recommended genotyping of acetylator status for optimization of INH dosing [26].

183

184 While there are significant differences in INH  $C_{max}$  and AUC observed between healthy adult volunteers  
185 and adults with TB/HIV and pediatrics with TB/HIV, our meta-analysis did not have a robust group of  
186 TB/HIV adult and pediatric patients; and therefore, these results and interpretations regarding TB/HIV  
187 patients should be extrapolated with caution. Nonetheless, healthcare providers should employ clinical  
188 judgments when treating the TB population.

189

190 For healthcare providers who are seeking to increase INH exposure for their patients, our meta-regression  
191 has shown that there is a dose proportional increase in INH  $C_{max}$  and AUC. However, with an INH dose  
192 increase there may be an increase in adverse events, although there are some data to support safety with  
193 high INH doses. Katiyar et al. reported that patients on INH dose range 16 – 18 mg/kg/day became  
194 sputum-negative 2.38 times faster than those patients who did not receive the high dose (5 mg/kg/day and  
195 placebo), and the high dose groups had more improved radiological imaging without the toxicity associated  
196 with INH [27]. A recent study of 59 TB patients were given a short course of INH dose range 5 – 15 mg/kg  
197 showed that 15.5% of patients had Grade 3 adverse events (pain, fever, dyspnea, pneumothorax, and  
198 anemia) and no cases higher than Grade 3; and the authors implied that these events were unlikely to be

199 related to study treatments. The 10 – 15 mg/kg INH doses were tolerable with pyridoxine co-administration  
200 [28]. High dose INH may be tolerable and safe, but clinicians should be cautious as more data is needed to  
201 further support this action.

202

203 NAT2 polymorphism should not be overlooked and must not be ignored given the results of this meta-  
204 analysis. Our meta-analysis showed a difference in INH PK due to NAT2 polymorphism and further  
205 stressed the need to test patients for NAT2 status. Patients with intermediate and fast NAT2 may have  
206 subtherapeutic exposure to INH with standard dosing, suggesting an INH dose of 800 mg/day, 500 mg/day,  
207 and 300 mg/day for fast, intermediate, and slow NAT2, respectively [29]. In a unique genotype-guided  
208 INH dosing study, patients were given either a standard INH dose (5 mg/kg) or an INH dose of 7.5 mg/kg,  
209 5 mg/kg, and 2.5 mg/kg for fast, intermediate, and slow NAT2 genotype, respectively. A lower incidence of  
210 adverse events in the genotype-guided group were reported compared to the standard dosing (5 mg/kg)  
211 group, although it was not statistically significant. The rate of INH-induced liver injury was zero in the  
212 slow NAT2 genotype-guided group (n = 7) whereas seven out of nine slow NAT2 patients in the standard  
213 group experienced INH-induced liver injury [30]. Testing patients for NAT2 status may be beneficial, cost-  
214 effective, and improve health outcomes [31], as an INH dose lower than 6 mg/kg would put a majority of  
215 fast NAT2 patients at a disadvantage and a 3 mg/kg dose would be sufficient for slow NAT2 patients and  
216 reduce INH toxicity [32]. Since the NAT2 genotype prevalence differs between countries, it is  
217 recommended that each country conduct a profiling study of NAT2 from its own population [33]. Results  
218 from genotyping or phenotyping of NAT2 were shown to be consistent when obtained from patients [34],  
219 and these tests may be recommended prior to treating TB patients with INH to steer the course of TB  
220 treatment.

221

222 **Conclusion**

223 While vast inter-study heterogeneity was present throughout this meta-analysis, this by itself does not  
224 compromise our results and implications. Heterogeneity is inherent in all meta-analyses, along with other  
225 factors, such as incomplete data, data conversion, and interstudy variation. Regardless, we believe that our  
226 meta-analysis highlights the differences in INH PK between healthy adult volunteers and TB patients,  
227 TB/HIV patients, and the importance of NAT2 polymorphism. These key results can be useful reference  
228 points for healthcare providers when dosing INH for treating TB patients. Future studies that assess INH  
229 pharmacodynamic and safety outcomes in TB treatment with regards to high-dose INH and NAT2  
230 polymorphism would be invaluable.

231

### 232 **Funding**

233 This work was supported in part by the Bill and Melinda Gates Foundation via a subaward of grant  
234 OPP1031105, awarded to the Critical Path to TB Regimens (CPTR) Initiative at the Critical Path Institute  
235 (C-Path).

236

### 237 **Supplementary Data**

238 Table S1 and Figure S1 are available as Supplementary Data.

239

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322 isoniazid acetylation in Polish tuberculosis patients. Biomed Res Int. 2013;2013:853602.

**Table 1.** Dose-normalized INH  $C_{max}$  for variables influencing its summary estimate.

Category	Number of study arms	Number of PK sets	$C_{max}$ estimates*	95% CI	I <sup>2</sup> (%)	P value
Adults						
Healthy volunteers	97	1180	1.089	(0.969, 1.209)	99.50	
TB only	57	1638	0.698	(0.637, 0.759)	96.86	<0.0001 <sup>a</sup>
TB/HIV	7	395	0.663	(0.567, 0.756)	90.95	<0.0001 <sup>a</sup> , 0.61 <sup>b</sup>
Pediatrics						
TB only	30	636	0.618	(0.517, 0.718)	99.49	<0.0001 <sup>a</sup> , 0.18 <sup>b</sup>
TB/HIV	5	119	0.498	(0.296, 0.699)	97.59	0.0025 <sup>a</sup> , 0.11 <sup>c</sup> , 0.34 <sup>d</sup>

Dose-normalization of  $C_{max}$  indicated significant differences between healthy adult volunteers and TB patients. No statistical significance is observed between TB adult patients and pediatric patients. (a) difference from healthy adult volunteers (b) difference from TB adult patients (c) difference from TB/HIV adult patients (d) difference from TB pediatric patients.

\* $C_{max}$  estimates are in ((mg/L)/(mg/kg))

**Table 2.** Dose-normalized INH AUC for variables influencing its summary estimate.

Category	Number of study arms	Number of PK sets	AUC estimates*	95% CI	I <sup>2</sup> (%)	P value
Adults						
Healthy volunteers	109	1267	4.329	(3.818, 4.840)	98.94	
TB only	45	1077	3.183	(2.804, 3.563)	98.50	0.0006 <sup>a</sup>
TB/HIV	4	189	2.503	(1.574, 3.431)	93.77	0.009 <sup>a</sup> , 0.18 <sup>b</sup>
Pediatrics						
TB only	20	322	2.695	(2.315, 3.075)	95.53	0.0002 <sup>a</sup> , 0.16 <sup>b</sup>
TB/HIV	3	90	1.674	(1.358, 1.990)	60.47	0.007 <sup>a</sup> , 0.22 <sup>c</sup> , 0.007 <sup>d</sup>

Dose-normalization of AUC indicated significant differences between healthy adult volunteers and TB patients. No statistical significance is observed between TB adult patients and pediatric patients. (a) difference from healthy adult volunteers (b) difference from TB adult patients (c) difference from TB/HIV adult patients (d) difference from TB pediatric patients.

\*AUC estimates are in ((mg·h/L)/(mg/kg))

**Table 3.** Effects of NAT2 polymorphism on dose-normalized  $C_{max}$  and AUC of all subjects

Category	Number of study arms	Number of PK sets	$C_{max}$ estimates*	95% CI	I <sup>2</sup> (%)	P value
NAT2 status						
Slow	46	830	0.946	(0.861, 1.032)	98.03	
Intermediate	9	219	0.733	(0.640, 0.826)	88.80	0.017 <sup>a</sup>
Fast	41	714	0.593	(0.511, 0.674)	98.46	<0.0001 <sup>a</sup> , 0.08 <sup>b</sup>
Category	Number of study arms	Number of PK sets	AUC estimates**	95% CI	I <sup>2</sup> (%)	P value
NAT2 status						
Slow	42	528	5.494	(4.796, 6.192)	99.18	
Intermediate	7	157	2.305	(1.755, 2.854)	97.52	<0.0001 <sup>a</sup>
Fast	35	497	2.017	(1.778, 2.255)	96.07	<0.0001 <sup>a</sup> , 0.27 <sup>b</sup>

Dose-normalization of  $C_{max}$  and AUC stratified by NAT2 status indicated significant differences between subjects with slow NAT2 and intermediate/fast NAT2 status. (a) difference from subjects with slow NAT2 status (b) difference from subjects with intermediate NAT2 status.

\* $C_{max}$  estimates are in ((mg/L)/(mg/kg))

\*\*AUC estimates are in ((mg·h/L)/(mg/kg))

## Figure Legends

**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for inclusion of isoniazid pharmacokinetic studies to February 2018.

**Figure 2.** Forest plot of dose-normalized AUC of adults with TB only. Study author, study arms, and year are listed. The black square and its size represent the mean and the sample size, with 95% CI as the horizontal line. The diamond is the summary estimate from all the study arms, and its expansion represents the 95% CI. The red-dotted line is a reference line with regards to the summary estimate.

**Figure 3.** Forest plot of dose-normalized AUC of pediatrics with TB only. Study author, study arms, and year are listed. The black square and its size represent the mean and the sample size, with 95% CI as the horizontal line. The diamond is the summary estimate from all the study arms, and its expansion represents the 95% CI. The red-dotted line is a reference line with regards to the summary estimate. **Figure 4. a)**

Forest plot of dose-normalized AUC of adults with TB/HIV. b) Forest plot of dose-normalized AUC of pediatrics with TB/HIV. Study author, study arms, and year are listed. The black square and its size represent the mean and the sample size, with 95% CI as the horizontal line. The diamond is the summary estimate from all the study arms, and its expansion represents the 95% CI. The red-dotted line is a reference line with regards to the summary estimate.

**Figure 5. a)** Meta-regression of  $C_{\max}$  with dose (mg/kg) as a covariate. A linear relationship is present with  $C_{\max}$  increasing as dose increases. Regression line is shown with equation. b) Meta-regression of AUC with dose (mg/kg) as a covariate. A linear relationship is present with AUC increasing as dose increases. Regression line is shown with equation, with corresponding p-value and  $R^2$ . Each circle represents a study arm and its size correlates to the sample size.

Figure 1.

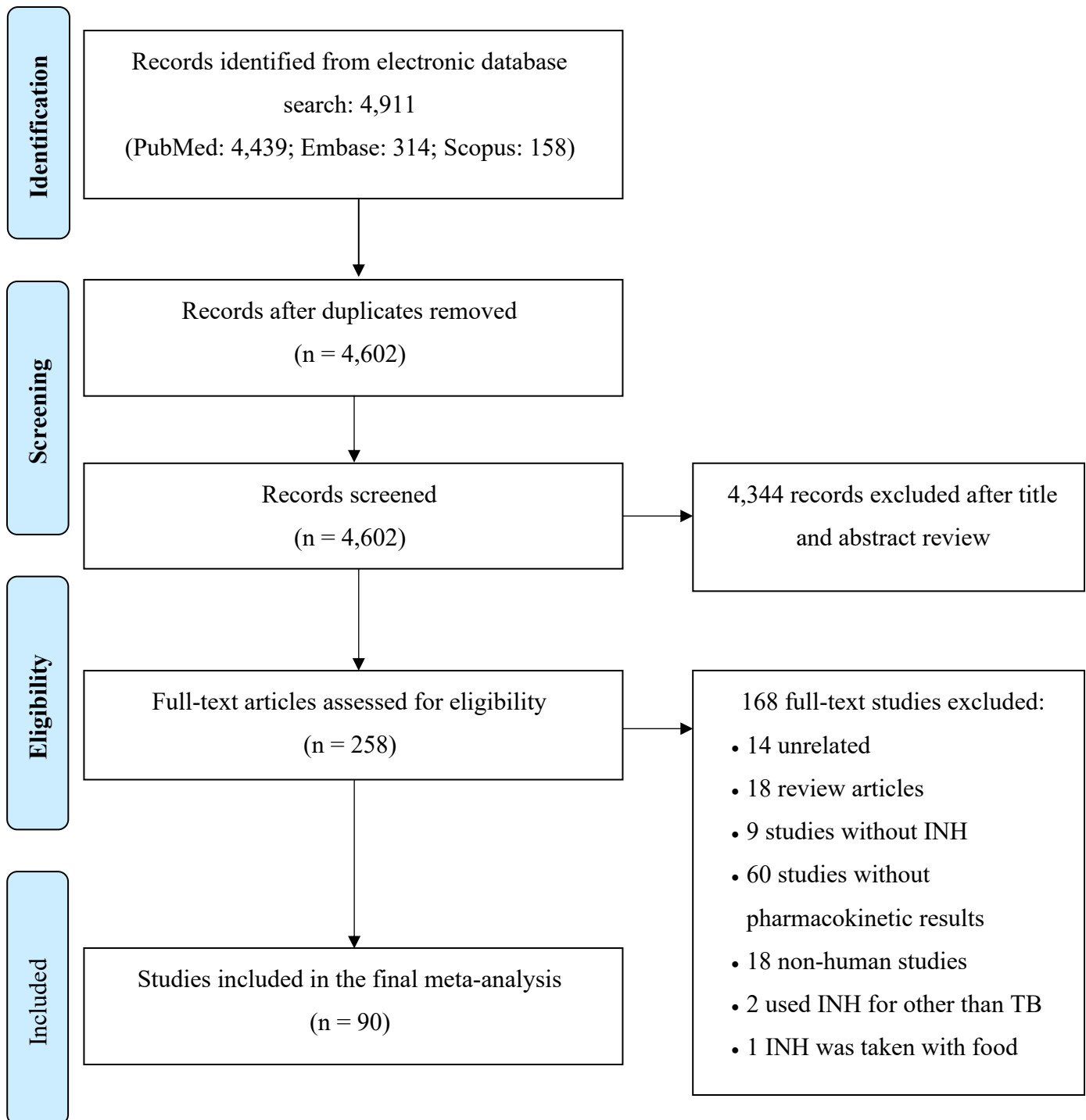


Figure 2.

Adults with TB

Studies	AUC Estimate (95% C.I.)
Tiitinen.1 1968	4.280 (2.813, 5.747)
Tiitinen.2 1968	8.280 (6.200, 10.360)
Advenier.1 1980	2.469 (1.707, 3.231)
Advenier.2 1980	4.900 (3.641, 6.159)
Ellard.1a 1986	1.840 (1.312, 2.368)
Ellard.2a 1986	1.820 (1.276, 2.364)
Ellard.3a 1986	4.400 (2.099, 6.701)
Ellard.4a 1986	4.500 (2.255, 6.745)
Ellard.5a 1986	2.253 (1.577, 2.930)
Ellard.6a 1986	2.320 (1.816, 2.824)
Garg.1 1988	5.343 (3.353, 7.334)
Garg.2 1988	3.994 (2.574, 5.414)
Garg.3 1988	7.361 (4.114, 10.608)
Garg.4 1988	4.771 (2.473, 7.069)
Gurumurthy.1 1990	5.065 (4.447, 5.683)
Gurumurthy.2 1990	2.338 (2.000, 2.676)
Shin 1990	2.266 (1.589, 2.943)
Walubo.1 1991	4.315 (3.897, 4.734)
Walubo.2 1991	4.835 (4.187, 5.484)
Walubo.1a 1991	3.677 (2.982, 4.372)
Walubo.2a 1991	4.079 (3.271, 4.888)
Walubo.3a 1991	4.954 (4.399, 5.508)
Walubo.4a 1991	5.112 (4.109, 6.115)
Smith 1994	2.947 (2.013, 3.880)
Parkin.1 1997	0.773 (0.600, 0.946)
Parkin.2 1997	1.652 (1.515, 1.789)
Parkin.3 1997	3.112 (2.933, 3.291)
Parkin.4 1997	0.462 (0.364, 0.560)
Parkin.5 1997	1.222 (1.112, 1.332)
Parkin.6 1997	2.836 (2.684, 2.988)
Augustynowicz-Kopec.1b 2002	1.581 (1.470, 1.693)
Augustynowicz-Kopec.2b 2002	3.490 (3.126, 3.854)
Weiner.1 2003	4.047 (3.373, 4.720)
Weiner.2 2003	3.400 (2.848, 3.952)
Weiner.3 2003	2.607 (1.966, 3.247)
Weiner.4 2003	4.080 (3.451, 4.709)
Weiner.5 2003	3.287 (1.872, 4.701)
Weiner.6 2003	3.253 (2.651, 3.856)
McIlleron 2006	5.000 (4.644, 5.356)
Singh 2007	2.453 (1.485, 3.421)
Thee.4 2010	3.240 (2.640, 3.840)
Babalik 2013	0.404 (0.256, 0.552)
Burham 2013	0.898 (0.445, 1.351)
Tostmann.1 2013	2.115 (1.700, 2.530)
Ooaterhout 2015	4.634 (3.774, 5.494)
Tappero.2 2005	2.754 (2.015, 3.493)
<b>Summary Estimate</b>	<b>3.183 (2.804, 3.563)</b>

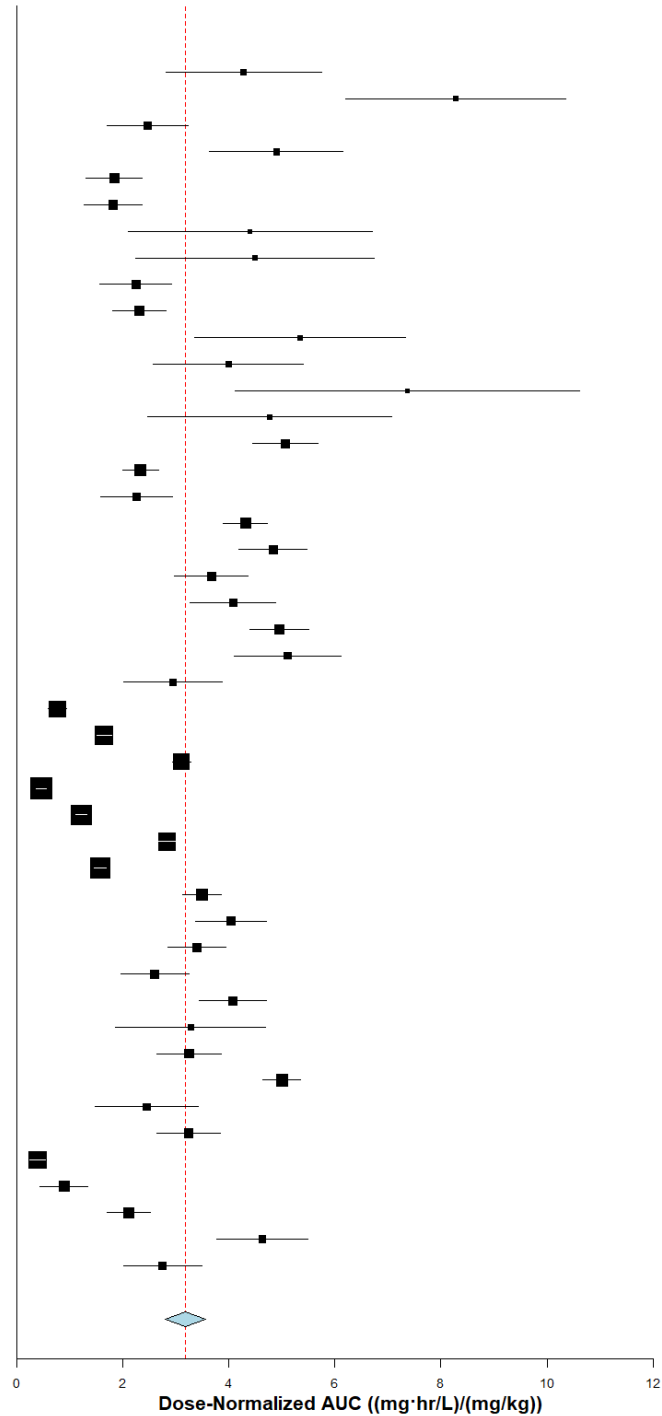


Figure 3.

**Pediatrics with TB**

Studies	AUC	Estimate (95% C.I.)
Eriksson.1 1988	2.090	(1.418, 2.762)
Eriksson.2 1988	1.930	(1.058, 2.802)
Eriksson.3 1988	1.770	(1.234, 2.306)
Eriksson.4 1988	2.100	(1.324, 2.876)
Roy.1 1995	6.129	(4.681, 7.577)
Roy.2 1995	5.314	(4.562, 6.066)
Rey.1 2000	3.594	(2.805, 4.383)
Rey.2 2000	1.836	(1.433, 2.239)
McIlleron.4a 2009	1.800	(1.365, 2.235)
Roy.1a 2009	4.600	(3.422, 5.778)
Roy.2a 2009	6.200	(5.022, 7.378)
Thee.1 2010	1.950	(1.283, 2.617)
Thee.2 2010	1.480	(0.976, 1.984)
Thee.3 2010	2.640	(1.664, 3.616)
Rangari.1a 2015	3.065	(2.959, 3.171)
Rangari.2a 2015	2.980	(2.763, 3.196)
Bekker 2016	1.928	(1.691, 2.165)
Kwara.1a 2015	1.719	(1.445, 1.994)
Antwi.1a 2017	1.858	(1.694, 2.021)
Mave.1 2017	2.187	(1.674, 2.700)
<b>Summary Estimate</b>	<b>2.695</b>	<b>(2.315, 3.075)</b>

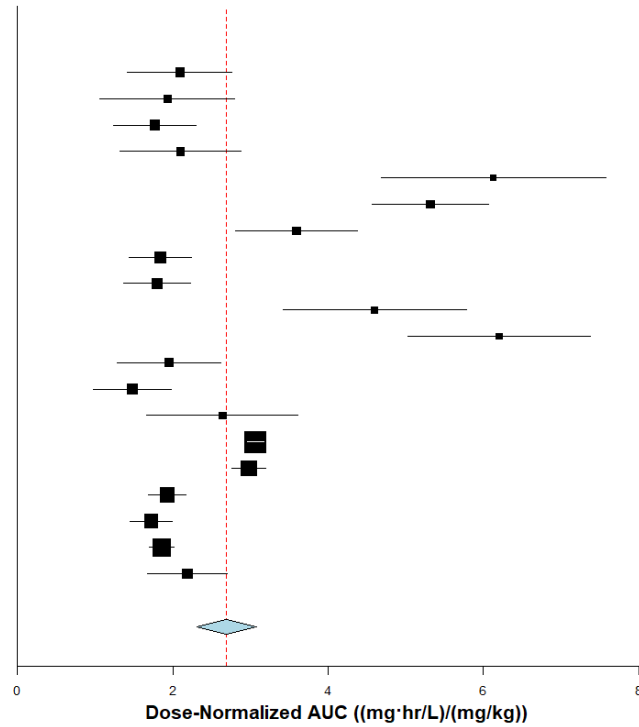
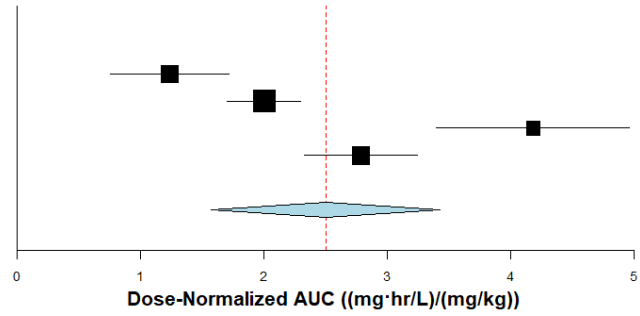


Figure 4.

**a) Adults with TB/HIV**

Studies	AUC Estimate (95% C.I.)
Weiner.1a 2005	1.233 (0.753, 1.713)
Weiner.2a 2005	2.000 (1.704, 2.296)
Bhatt 2013	4.184 (3.401, 4.967)
Tappero.1 2005	2.785 (2.325, 3.244)
<b>Summary Estimate</b>	<b>2.503 (1.574, 3.431)</b>



**b) Pediatrics with TB/HIV**

Studies	AUC Estimate (95% C.I.)
Kwara.2a 2015	1.408 (1.116, 1.699)
Antwi.2a 2017	1.842 (1.575, 2.109)
Mave.2 2017	1.832 (1.296, 2.368)
<b>Summary Estimate</b>	<b>1.674 (1.358, 1.990)</b>

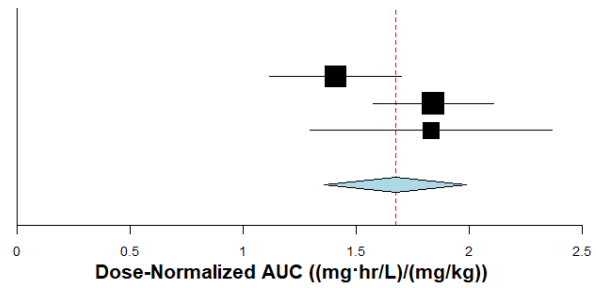
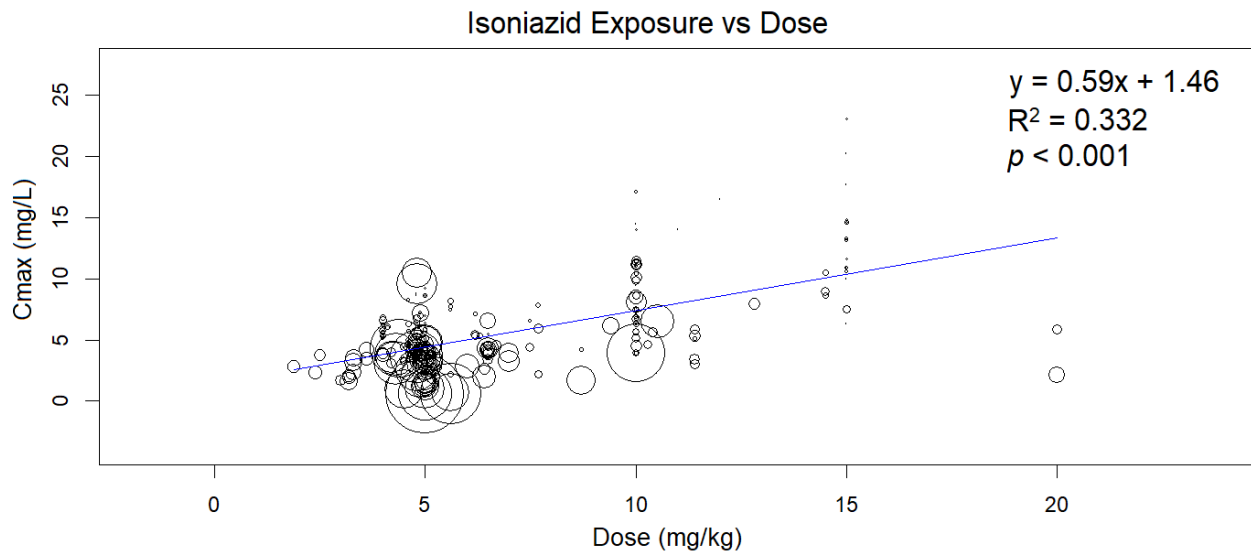


Figure 5.

a)



b)

