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Clinical Risk Factors for Multi-Drug Resistance Tuberculosis in Ethiopia: A Meta-Analysis

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ABSTRACT

Background: The main purpose of this meta-analysis is to evaluate the association between clinical risk factors and multi-drug resistance tuberculosis. More specifically, it tried to measure the association of the risk of MDR-TB with HIV serostatus, previous anti-TB, contact history with known TB case and with known MDR-TB case.

Methods: A separate meta-analysis was done for commonly reported clinical risk factors of MDR-TB. Literature search strategy includes searching PubMed/Medline, HINARI, EMBASE, and the Google scholar using keywords. Researches written in English, done in Ethiopia, observational studies which assessed the association of MDR-TB with at least one of the most commonly reported clinical risk factors were included. Rev Man 5 used to analyze data. The pooled OR estimated with random-effects model using the Mantel-Haenszel method. The heterogeneity among the studies was assessed with chi-square, I² and p-values. Publication bias was assessed with funnel plots and trim-and-fill analysis was done with STATA 11 to adjust the report bias.

Results: The effect of HIV on MDR-TB was not statistically significant both before [pooled-OR=1.63, 95%CI: 0.76, 3.49] and after [pooled-Log-OR=-0.133, 95%CI: -0.921, 0.654] trim-and-fill analysis. Previous anti-TB treatment is a risk factor for MDR-TB before [pooled-OR=7.63, 95%CI: 3.76, 15.5] and after trim-and-fill [pooled-Log-OR=1.156 95%CI: 0.394, 1.918]. Contact history to TB patient is a risk factor for MDR-TB before [pooled-OR=2.04, 95% CI: 1.57, 2.65] and after trim-and-fill analysis [pooled-Log-OR=0.641, 95%CI: 0.420, 0.682]. Contact history to MDR-TB patient is also found to be a risk factor for developing MDR-TB before trim-and fill [pooled-OR=2.85, 95%CI: 1.82-4.44].

Conclusion: Except HIV, previous anti-TB treatment, contact with TB and MDR-TB patients are risk factors of MDR-TB. Infection prevention and anti-TB drug management should be strictly practiced. A legal framework for anti-TB drug management practice should be designed. Further synthesis of evidence should be conducted using meta-regression.

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Introduction

Drug-resistant tuberculosis (DR-TB) presents new barriers to the control of TB worldwide [1]. It is a man-made problem, largely as consequence of human error in quality of anti-TB drugs and patient treatment [2].

According to the World Health Organization's (WHO), globally, nearly half a million cases of MDR-TB emerge every year and 110,000 die annually [3]. In the year 2006, MDR-TB among newly diagnosed and previously treated TB cases were 3.1% and 19.3%, respectively, with a global 4.8% incident MDR-TB case [4,5].

Multidrug-resistant TB among new cases in the WHO African Region was seen lowest (0.7%) in Madagascar and highest (3.9%) in Rwanda, In South-East Asia, it was seen lowest (0.2%) in Sri Lanka and highest (4.0%) in Myanmar [6,7].

Ethiopia is one of the 27 high MDR-TB burden countries; it is ranked 15th with more than 5000 estimated MDR-TB patients each year [8]. The appearance and spread of drug-resistant TB strains in new and previously treated cases worsens the existing TB problem in Ethiopia [9]. Between the years 2007 and 2012, a total of 1144 MDR-TB cases were reported, in Ethiopia. After, declined from 145 in 2007 to 130 in 2008, increasing trend from 130 to 284 cases of MDR-TB among all cases, during 2008 to 2012 was observed [10,11].

The MDR-TB proportion among all TB cases varies from place to place. A study done in Addis Ababa reported 12% MDR-TB cases [12]. Agonafir et al. reported 43% MDR-TB and 4.4% XDR-TB in 2010 [13]. A study from northwest Ethiopia showed 5% of MDR-TB [14]. Study in three sites of Bahir Dar indicated 11.8% MDR-TB and 1% XDR-TB cases [15]. By the year 2012, a study from Addis Ababa reported 46.3% of MDR-TB among all retreated cases from 2004 to 2008 [16]. Another study from northwest Ethiopia reported 11.54% of MDR-TB patients [17]. Studies in other parts

of the country indicated 1.3%, 6.5% and 3.3% of MDR-TB [18-20]. A study conducted in 2008 reported 32.8% MDR-TB case [21].

Several factors accounted for the spread of MDR-TB. Studies reported that newly treated TB cases can also harbor MDR-TB, previous exposure to TB treatment was the most significant risk factor in Ethiopia [2,14,22-25]. Studies also showed HIV as risk factor for MDR-TB [26-28]. However, study results in East Africa not reported a positive association between HIV and MDR-TB [2,14,22,25].

In the context of Ethiopia, a systematic review without meta-analysis conducted by weldegebreal, et al. focused on the magnitude and factors of multi- drug resistance [29]. Another review by Biadlegne, et al. have been largely limited to any drug resistance TB situation without meta-analysis [30]. The systematic reviews with meta-analysis were conducted by Eshetie et al and Mesfin et al [31,32]. The first focused on pooling the magnitude of MDR-TB and quantified the effect of previous anti-TB treatment on MDR-TB. The second however measured the association between HIV and MDR-TB globally and not specific to Ethiopian context. Moreover, a meta-analysis by Berhan et al pooled the effect of both previous anti-TB treatment and HIV on MDR-TB in Sub-Saharan countries [23].

However, the findings of the pooled estimate of the association between HIV and MDR-TB contradicts that in Mesfin et al reported as it is a risk factor while the other by Berhan et al it is not. In addition, all are conducted before three years and not updated yet. To date, there is no published meta-analysis that included the most recent studies exclusively in Ethiopia, which have assessed the association of clinical risk factors with multidrug-resistant TB. Thus, the primary aim of this meta-analysis hence was to determine how strongly multidrug-resistant TB is associated with history of contacts of known MDR-TB case, previous exposure to TB treatment, HIV co-infection and history of contacts with known TB case in Ethiopia.

Methods

Criteria for considering studies for this meta-analysis

Types of studies: Research works considered for inclusion in to this meta-analysis were cross-sectional and case-control researches which assessed the association of multidrug resistant tuberculosis with at least one of the most commonly reported clinical risk factors such as; HIV co-infection, previous exposure to TB treatment, history of contacts to known TB case and history of contacts to known MDR-TB case.

Types of data: Only the categorical or dichotomous data were used in the analysis. These includes number of individuals on MDR-TB in HIV positives VS MDR-TB in HIV negatives; MDR-TB in previous exposure to TB treatment VS MDR-TB in no previous exposure to TB treatment; MDR-TB in contacts history with TB case Vs MDR-TB in no contacts history with TB case and MDR-TB in contacts history with MDR-TB case Vs MDR-TB in no contacts history with MDR-TB case.

Types of methods: Those studies employed the binary logistic regression method of analysis to estimate the effect size of the measure of association (both the crude odds ratio in bivariable and the adjusted odds ratio in multiple variable binary logistic regressions) were included in this analysis.

Types of outcome measures: only those studies which were used and reported the adjusted odds ratio to measure the association

between at least one of the clinical risk factors and the outcome MDR-TB were considered. The primary outcome of the analysis was presence of MDR-TB.

Search methods for identification of studies

The search methods include a computer based electronic searches for bibliographic databases sources and electronically available full text journals. In addition google scholar search engine for searching other resources and Internet citation search strategy of relevant articles for the non-bibliographic database sources were used.

Electronic searches: A computer based electronic searches includes searching of an electronic database sources of PubMed/MEDLINE, HINARI and EMBASE. Furthermore, the general search engine of Google scholar used to search electronically available full text journals and cited references. The search strategy used MeSH terms combined with keywords such as “Resistance TB”, “MDR-TB”, “Risk Factors”, “TB-Treatment History”, “TB-Contact History”, “Acquired MDR-TB”, “Transmitted MDR-TB”, “Ethiopia” and “the names of Ethiopia National Regional States”. Each term was searched separately with the name of the study region. The four authors were independently search for all of the keywords in the databases and cited references. Each source were search from October, 2019 to September, 2020.

Selection of studies: To select studies four authors independently scrutinize titles/abstract lists from the literature searches. Studies considered relevant in terms of title and abstract were searched in full-text. The full- text article was retrieved even if only one of the scrutinizers considers that full-text reading was warranted. The scrutinizers then decide independently whether the articles retrieved were relevant to the research question and meet any other inclusion criteria. The scrutinizers then compared their inclusion lists. If the lists were not in agreement, then together the scrutinizers discuss the papers and reach consensus as to whether or not the article should be included.

Data extraction and management: The reviewers carried out the data extraction carefully & critically looking in to each research work included for this meta-analysis and filling the data obtained in to the data extraction instrument (check list) developed in Excel spreadsheet. The data extraction includes variables such as the author(s) of the article, the place where the study was conducted, year of publication, number of MDR-TB patients in HIV positives, number of MDR-TB patients in HIV negatives, number of MDR-TB patients with previous anti-TB drug treatment history, number of MDR-TB patients with no previous anti-TB drug treatment history, MDR-TB patients with contact history of known TB patients, number of MDR-TB patients with no contact history of known TB patients, number of MDR-TB patients with contacts history of known MDR-TB patients, number of MDR-TB patients with no contacts history of known MDR-TB patients were extracted for analysis.

Data analysis: Data analysis was performed using the RevMan software. The associations of multidrug- resistant TB with history of contacts of known TB case, history of contacts of known MDR-TB case, previous exposure to TB treatment, HIV co-infection, were meta-analysed separately. The overall odds ratios were determined with the Der Simonian- Laird method (random-effects model). The Mantel-Haenszel method of analysis, in Rev Man was used to estimate the pooled estimate of the respective risk factors’ odds ratios.

Assessment of heterogeneity: The heterogeneity among the studies was assessed by computing values for chi-square (Q), I² and p-values. I² ≥ 50% was considered as statistically significant and hence had heterogeneity.

Subgroup analysis: To reveal the change in multidrug resistant TB with study types, sub-group analyses based on study design was carried out (Case-Control Vs Cross-sectional) particularly for the pooled estimate of the association between HIV infection, previous anti-TB treatment and MDR-TB.

Sensitivity analysis: Sensitivity analyses (leaving one study out at a time) were conducted to estimate the stability of the overall odds ratios in the withdrawal of any studies from the analysis and it was found not has significant change on the pooled odds ratio.

Assessment of reporting biases: Publication/disclosure biases were assessed with funnel plots. For those funnel plot results of asymmetric distributions, suggesting publication bias, a Trim and fill analysis was used to further assess the bias due to publication, to estimate the missed number of studies and to fill in order to adjust for the theoretically unpublished articles. The funnel plot assessment of reporting bias and the Trim-and-Fill analysis were done using STATA version 11 since Rev Man has no such built-in programs or packages for Trim-and-Fill analysis.

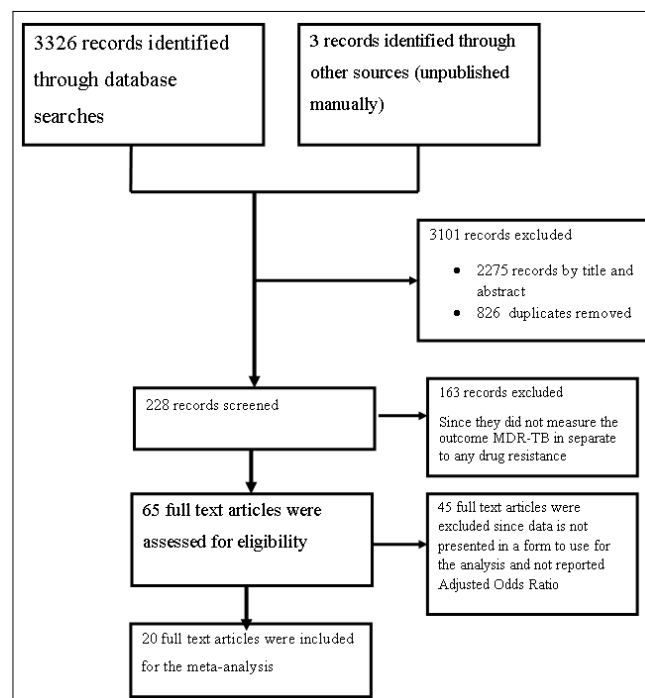


Figure 1: Study flow diagram (PRISMA flow chart)

Result

Search Result

The total numbers of databases identified through search were 3329. About 826 studies were removed since found duplicated and 2275 studies were excluded by their titles and abstracts. About 228 studies were screened and 163 studies were excluded since did not met the inclusion criteria. About 65 full articles were further assessed for eligibility among the four investigators individually and 45 articles were excluded since the data is not presented in the form to do meta-analysis and 20 studies were included in the meta-analysis (Figure 1).

Studies which assessed at least one of the most commonly reported clinical risk factors for MDR-TB such as HIV, previous anti-TB treatment history, contact history with known TB case and contact history with known MDR-TB case were included in the analysis and a separate meta-analysis was done for each risk factor. Among 20 studies included in the analysis 11 were case-control studies and the rest 9 were cross-sectional [14,19,26,27,33-48]. About eight studies, 6 case-control and 2 cross-sectional were included for at least two clinical risk factors and the rest 12 studies for only one risk factor [14,19,33,34,38-48] (Table 1).

Table 1: The Characteristics of Studies included for the meta-analysis of the effect of clinical risk factors on MDR-TB, Ethiopia, 2021

Study Author/s	Year published	Place conducted	Study design	Assessed clinical Risk Factor			
				HIV status	Previous Anti-TB	Contact with TB patient	contact with MDR-TB
Sefonias Getachew	2012	Addis Ababa	case control	yes	no	yes	yes
Tessema et al	2012	Amhara region	cross-sectional	yes	no	no	no
Hirpa et al	2013	Addis Ababa	case control	yes	no	no	no
Abdella, K. et al	2015	Jimma	cross-sectional	yes	no	no	no
Gashaw et al	2015	Dessie City	cross-sectional	yes	no	no	no
Mulisa et al	2015	Oromia	case control	yes	no	no	no
Dessalegn et al.	2016	Addis Ababa	case control	yes	yes	no	no
Workicho et.al	2017	Addis Ababa	case control	yes	yes	no	no
Teabie Tsega et al	2017	Debre Markos	cross-sectional	yes	yes	no	no
Mesfin, E. A et al	2018	Addis Ababa	cross-sectional	yes	yes	no	no
Babure et al	2019	Nekemt	case control	yes	yes	no	no
Desissa et al.	2018	Bishoftu	case control	no	yes	yes	no
Hamusse S.D et al	2016	Hitossa	cross-sectional	no	yes	no	no
Mulu W et al	2015	Amhara region	case control	no	yes	no	yes
Esmael A et al	2014	Amhara region	cross-sectional	no	yes	no	no

Nigus et al	2014	Amhara region	cross-sectional	no	yes	no	no
Mekonnen et al	2015	Metema	cross-sectional	no	yes	no	no
Assefa et al	2017	Addis Ababa	case-control	no	no	yes	no
Gobena, D et al.	2018	Jimma	case_control	no	no	no	yes
Fikre A et al.	2019	South Ethiopia	case_control	no	no	no	yes

Effects of HIV on MDR-TB

Eleven studies, six case-controls and five cross-sectional with total sample size of 2551 were included for the pooled analysis of the effect of HIV sero-status on MDR-TB [14,26,27,36,37,39,41-43,46,48]. The characteristics of the included studies were presented in (Table 2).

Table 2: The Characteristics of Studies included for the meta-analysis of the effect of HIV sero-status on MDR-TB, Ethiopia, 2021

Study Author/s	Year published	Place conducted	Study design	MDR-TB in HIV+		MDR-TB in HIV-		Sample size
				Yes	No	Yes	No	
Sefonias Getachew	2012	Addis Ababa	case control	27	25	50	117	215
Tessema et al	2012	Amhara region	cross-sectional	4	62	9	185	260
Hirpa et al	2013	Addis Ababa	case control	18	40	116	94	268
Abdella, K. et al	2015	Jimma	cross-sectional	10	13	11	36	70
Gashaw et al	2015	Dessie City	cross-sectional	4	106	3	319	432
Mulisa et al	2015	Oromia	case control	17	55	70	84	226
Dessalegn et al.	2016	Addis Ababa	case control	19	48	84	55	206
Workicho et.al	2017	Addis Ababa	case control	45	26	45	64	180
Teabie Tsega et al	2017	Debre Markos	cross-sectional	12	17	36	338	403
Mesfin, E. A et al	2018	Addis Ababa	cross-sectional	71	57	18	80	226
Babure et al	2019	Nekemt	case control	11	8	10	36	65
Total				238	457	452	1408	2551

The pooled estimate of the odds ratio showed that there is no statistically significant association between HIV sero-status and the risk of developing MDR-TB (pooled OR=1.63, 95%CI: 0.76-3.49). The sub-group analysis, by type of study design clearly indicated that though the overall effect is not statistically significant, the case-control studies tends to report the reduced effect of HIV positivity on the risk of developing MDR-TB (sub-group pooled OR=0.94, 95%CI: 0.27-2.38) while the cross-sectional studies tends to report a statistically significant increased risk of developing MDR-TB among HIV positives (sub-group pooled OR=3.59, 95%CI: 1.93-6.65) (Figure 2).

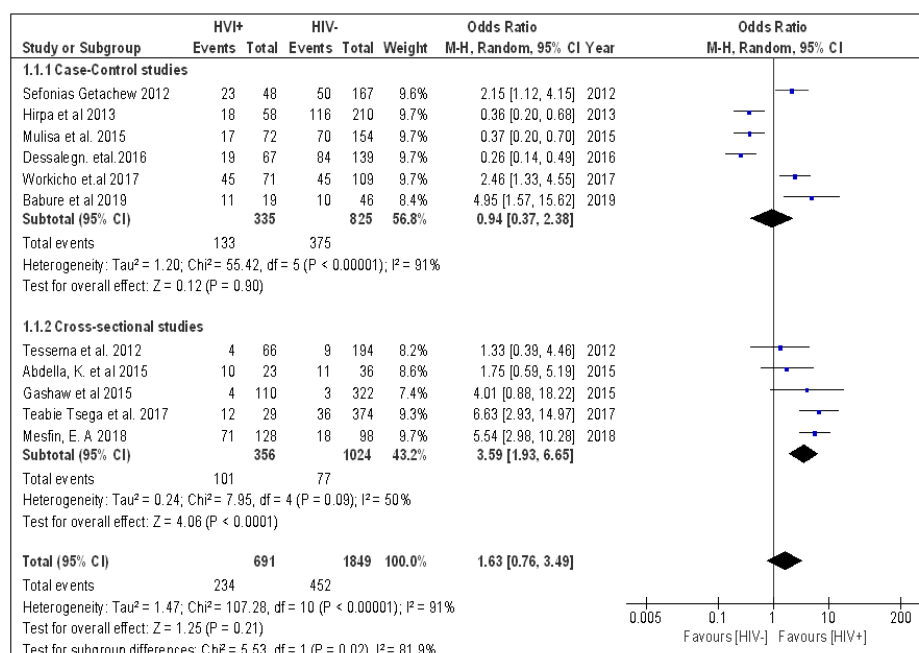


Figure 2: A sub-group analysis Forest plot of comparison of effect of HIV positive Vs HIV negative on the risk of developing MDR-TB. Ethiopia 2021.

The overall heterogeneity of the studies was assessed and found to be substantial. The variance between studies ($\tau^2=1.47$), test for significance difference between the studies ($\chi^2=107.28$, $p<0.00001$) and the percentage variation is high ($I^2=91\%$). In addition the heterogeneity due to publication bias was assessed through funnel plot. The plot findings were indicative of presence of publication bias as an extremely asymmetrical distribution of studies on the plot was observed. The funnel plot was done by study types. Though it was observed that the asymmetry is to the right side for the overall studies, as it was observed in the funnel plot by study types, most cross-sectional studies were distributed on the right side of the overall effect size (pooled log OR) but three case-control studies each distributed on either side of the pooled effect size (Figure 3).

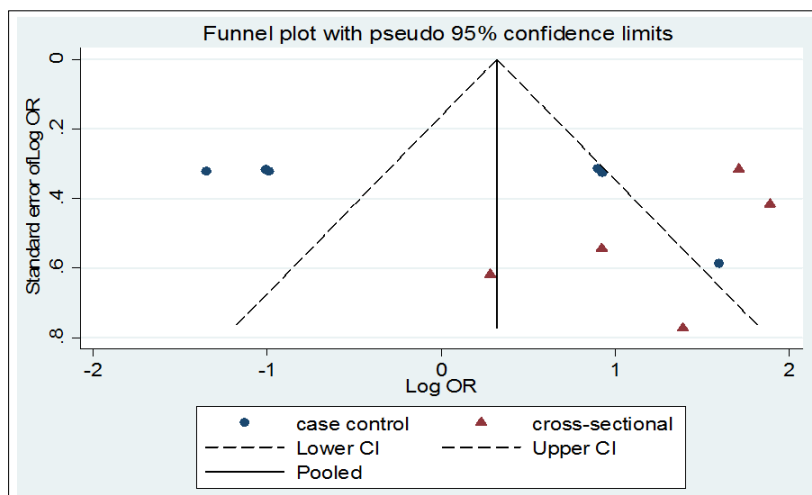


Figure 3: Funnel plot with pseudo 95% confidence limits of studies in the pooled analysis of effects of HIV sero-status on MDR-TB by Study type, Ethiopia 2021

To adjust for publication bias trim and fill analysis was done using metatrim command in stata version 11. The findings of the trim and fill analysis indicated that before removal of the four studies distributed on the right side of the funnel plot the pooled estimate (Pooled Log OR) was found 0.534 (95%CI: -0.236-1.304) in random effect model, which is equivalent to a pooled OR of 1.706 (95%CI: 0.79, 3.684). Furthermore, in the filled meta-analysis following replacing the removed four studies and adding other four studies substituting for unpublished articles the pooled estimate (Pooled Log OR) was found -0.133 (95%CI: -0.921, 0.654) in random effect model, which is equivalent to a pooled OR of 0.875 (95%CI: 0.398, 1.923). This showed a decrease of the pooled OR from 1.63 to 0.875 following a trim-and-fill analysis in random effect model. It was -0.20 (95%CI: -0.4, 0.001) in fixed effect model, similar to an overall OR of 0.819 (95%CI: 0.670, 1.001). This showed a decrease of the pooled OR from 1.63 to 0.819 following a trim-and-fill analysis in fixed effect model (Figure 4 & Figure 5).

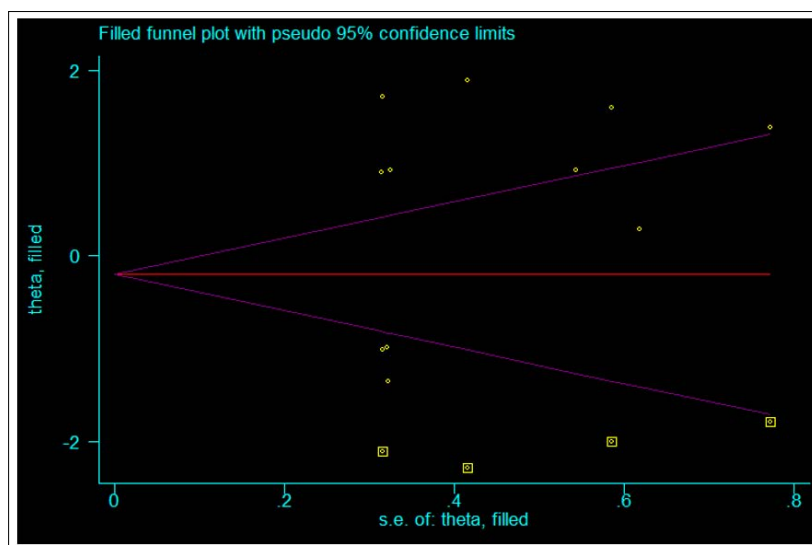


Figure 4: Filled funnel plot with pseudo 95% confidence limits for the log odds ratio of HIV Sero-Status effect on developing MDR-TB, the circular dots indicate the observed studies and the square dots indicate the missing studies imputed by the trim-and-fill method (based on the linear estimator), Ethiopia, 2021.

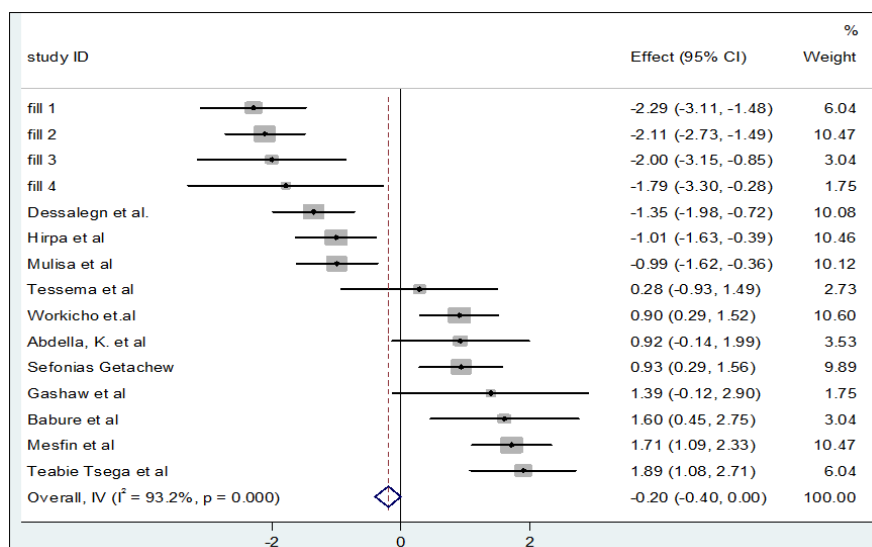


Figure 5: A forest plots of studies for the pooled log odds ratio of the effect of HIV sero-status on MDR-TB following trim and fill analysis, Ethiopia, 2021

Effects of previous Anti-TB treatment on MDR-TB

About 11 studies, 5 case-control and 6 cross-sectional, with total sample size of 2671 were considered eligible for meta-analysis for the assessment of the effect of History of previous anti-TB treatment on MDR-TB (Table 3) [19,26,27,35,36,41,44-48].

Table 3: The Characteristics of Studies included for the meta-analysis of the effect of History of previous anti-TB treatment on MDR-TB, Ethiopia, 2021

Study Author	year Published	place conducted	Study design	MDR-TB In Retreated		MDR-TB In New cases		Sample size
				Yes	No	Yes	No	
Babure et al	2019	Nekemt	case control	15	3	6	41	65
Desissa et al.	2018	Bishoftu Hospital	case control	48	30	25	116	219
Hamusse S.D et al	2016	Hitossa	cross-sectional	3	18	2	83	106
Workicho et.al	2017	Addis Ababa	case control	82	30	8	60	180
Mulu W	2015	Amhara region	case control	147	131	6	22	306
Esmael A et al	2014	Amhara region	cross-sectional	12	53	3	162	230
Desalegn et al.	2016	Addis Ababa	case control	96	25	7	78	206
Teabie Tsenga et al	2017	D/Markos	cross-sectional	31	80	17	275	403
Mesfin, E. A	2018	Addis Ababa	cross-sectional	73	89	16	48	226
Nigus et al	2014	Amhara region	cross-sectional	97	432	13	64	606
Mekonnen et al	2015	Metema	cross-sectional	5	31	2	86	124
Total				609	922	105	1035	2671

The result below in Figure 6 showed that history of previous anti-TB treatment has statistically significant association with the risk of developing MDR-TB. The sub-group analysis by type of study indicated that the pooled OR in the case-control studies was high in magnitude but less precise as the confidence interval is wider (Pooled OR=14.68, 95%CI: 6.17-34.95). However, the pooled OR in the cross-sectional studies was small in magnitude but greater in precision (Pooled OR=4.02, 95%CI: 1.83-8.83). The overall pooled odds ratio was 7.63 (95%CI: 3.76, 15.5) (Figure 7).

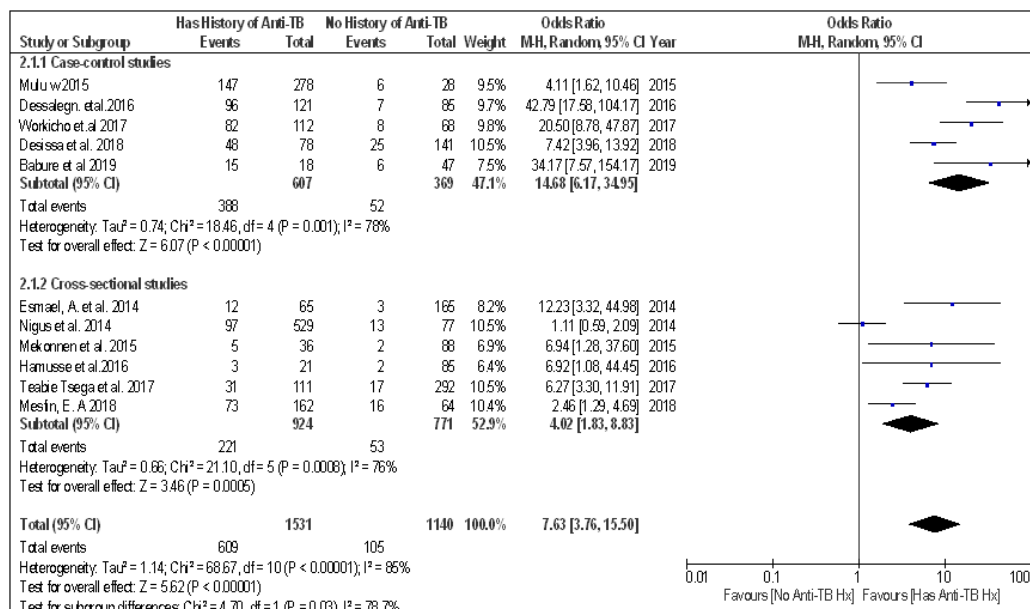


Figure 6: Forest plot of comparison of the effect of having previous history of Anti-TB treatment Vs without History of Anti-TB treatment on MDR-TB, Ethiopia 2020

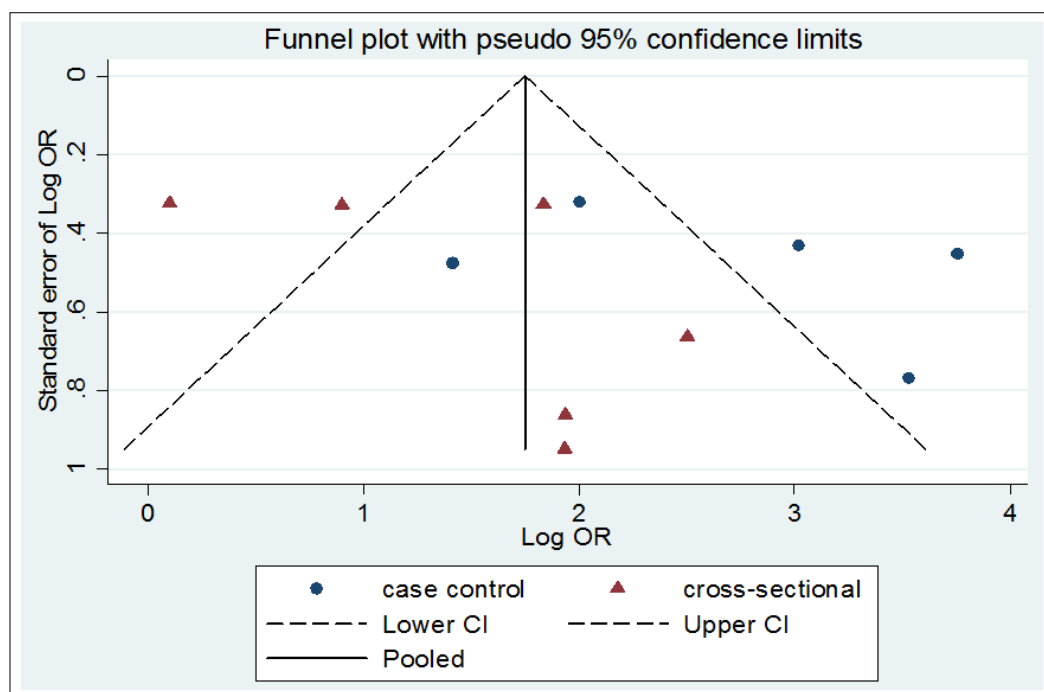


Figure 7: funnel plots with pseudo 95% confidence interval of studies in the pooled analysis of the effect of previous anti-TB treatment history on the development of MDR-TB by the study type.

To deal with heterogeneity a sub group analysis by type of study was conducted, however, it was found substantial both for the subgroups (case-control, $I^2=78\%$ and cross-sectional, $I^2=76\%$) and the overall heterogeneity ($I^2=85\%$). The publication bias was also assessed with funnel plots and the result indicated that most (4 of the 5) case-control studies were distributed on the right side of the pooled log odds ratio while two of the six cross-sectional studies effect size distributed on the left side of the pooled log odds ratio. The overall assessment showed presence of publication bias since there is a huge asymmetrical distribution of the studies in the funnel plot below (Figure 7).

Trim and fill analysis was done to adjust the publication bias. In the analysis before removal of the five studies with extreme effect size (log odds ratio) in the funnel plot the pooled estimate (Pooled Log OR) was 2.032 (95%CI: 1.324-2.741) in random effect model. Furthermore, in the filled meta-analysis following replacing the former removed five studies after application of an iterative algorithm and adding other five studies substituting for the theoretical unpublished articles the pooled estimate (Pooled Log OR) was 1.156 (95%CI: 0.394, 1.918) in random effect model, which is equivalent to a pooled OR of 3.18 (95% CI: 1.48, 6.81), this showed a decrease in magnitude of pooled odds ration from 7.63 to 3.18 following trim-and fill analysis. Similarly, the Pooled Log OR was 1.070 (95%CI: 0.854, 1.285) in fixed effect model, which is equivalent to a pooled OR of 2.92 (95% CI: 2.349, 3.615), this showed a decrease in magnitude of pooled odds ration from 7.63 to 2.92 following trim-and fill analysis (Figure 8 & Figure 9).

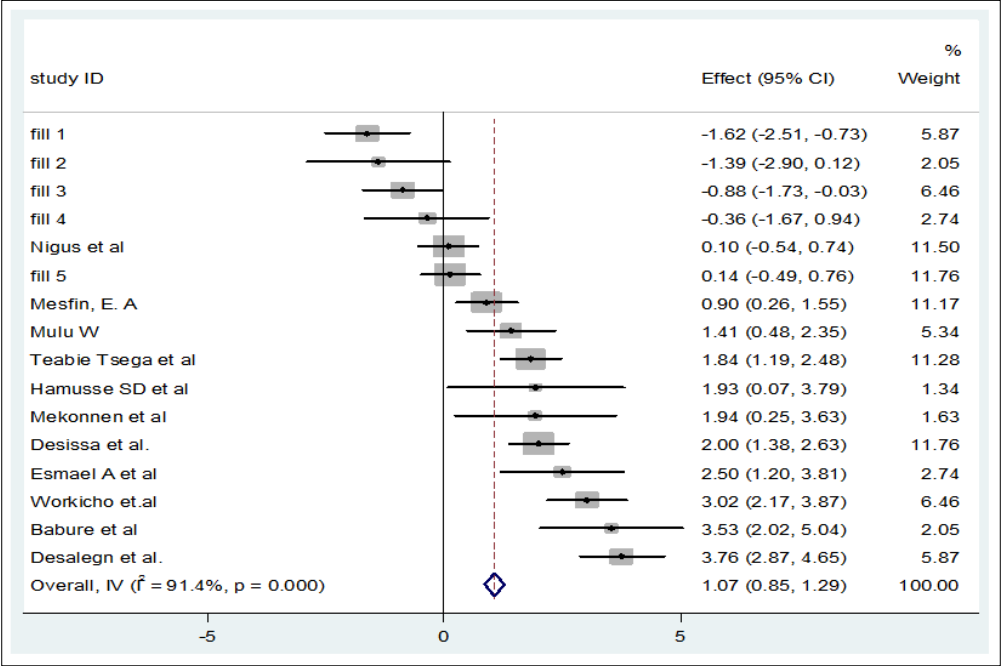


Figure 8: A forest plots of studies for the pooled log odds ratio of the effect of Previous Anti-TB treatment History on MDR-TB following trim and fill analysis, Ethiopia, 2021

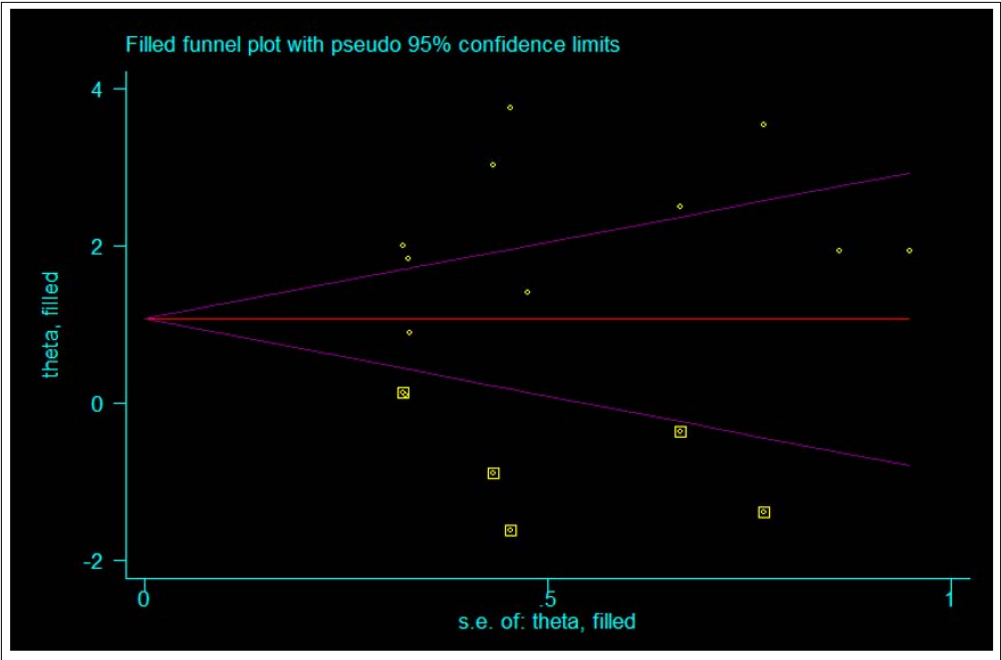


Figure 9: Filled funnel plot with pseudo 95% confidence limits for the log odds ratio of previous anti-Tb treatment history effect on developing MDR-TB, the circular dots indicate the observed studies and the square dots indicate the missing studies imputed by the trim-and-fill method (based on the linear estimator), Ethiopia, 2021

Effects of Contac History to known Tuberculosis patient on MDR-TB

Only three studies with total sample size of 1, 138, all case-control were found eligible for meta-analysis to measure the effect of contact History to a known tuberculosis patient on the risk of developing MDR-TB (Table 4) [34,35,37].

Table 4: The Characteristics of Studies included for the meta-analysis of the effect of History of contact to known-TB patient on the risk of developing MDR-TB, Ethiopia, 2021

Study Author	year Published	place conducted	Study design	MDR-TB with contact History		MDR-TB with no contact History		Sample size
				Yes	No	Yes	No	
Sefonias Getachew	2012	Addis Ababa	case-control	30	36	40	103	209
Assefa et al	2017	Addis Ababa	case-control	91	124	138	357	710
Desissa et al.	2018	Oromia	case-control	45	58	28	88	219
Total				166	218	206	548	1138

The pooled odds ratio of contact history with known pulmonary tuberculosis patient was found statistically significantly associated with the risk of developing MDR-TB. The result below showed that individuals who had contact history were 2.04 times more at risk of developing MDR-TB compared to those who did not have contact history with a known tuberculosis patient (Pooled OR=2.04, 95% CI: 1.57, 2.65) (Figure 10).

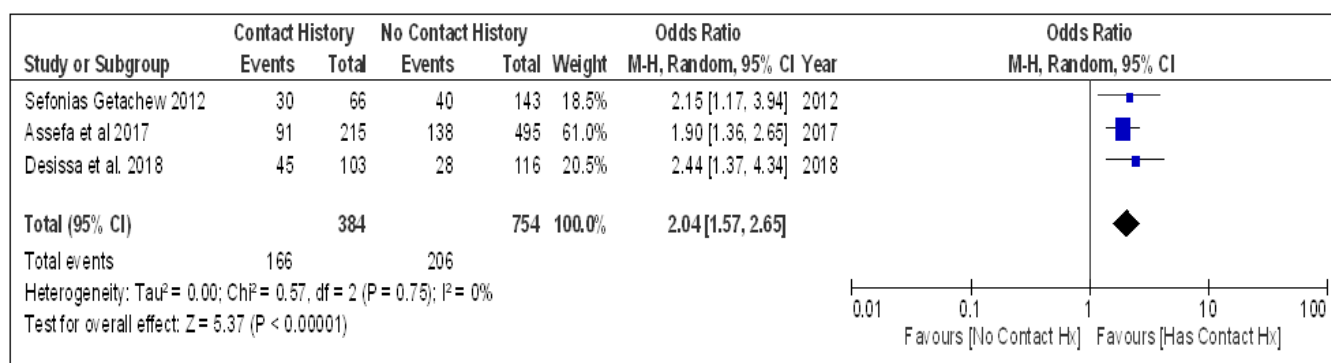


Figure 10: Forest plot of comparison of effect of having Contact History Vs without contact History to a known tuberculosis patient on MDR-TB, Ethiopia, 2020

The publication bias was assessed with funnel plot and it indicates presence of bias due to the asymmetric distribution of the studies' effect size around the pooled log odds ratio, two being resided on the right side and bottom level of the funnel plot while only one is on the left side with a relatively minimum standard error (Figure 11).

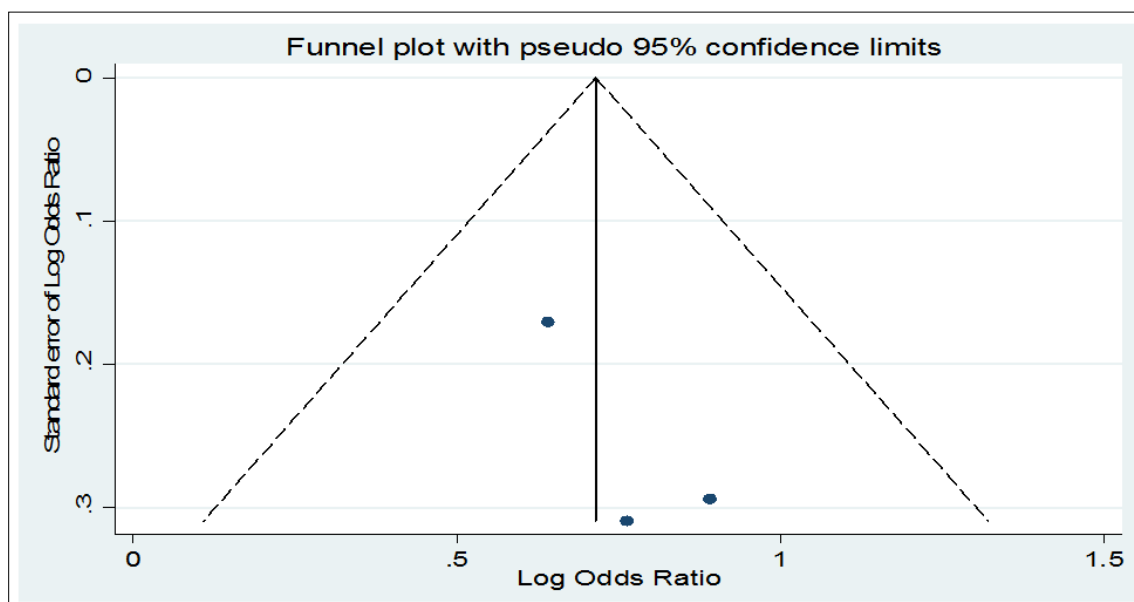


Figure 11: funnel plots with pseudo 95% confidence interval of studies in the pooled analysis of the effect of TB contact history on the development of MDR-TB, Ethiopia, 2021

In order to adjust for the publication bias trim and fill analysis was used. In the analysis before removal of the outlier effect size the pooled estimate (Pooled Log OR) was 0.715 (95%CI: 0.454-0.976) in random effect model. In the filled meta-analysis following replacing the previously trimmed two studies and adding other two studies accounting for the theoretical unpublished articles the pooled estimate (Pooled Log OR) was 0.641 (95%CI:0.420-0.682) both in random and fixed effect model. It was also found that after the trim and fill analysis the heterogeneity test was not significant ($I^2=0.0\%$, $P=0.78$) (Figure 12 and Figure 13).

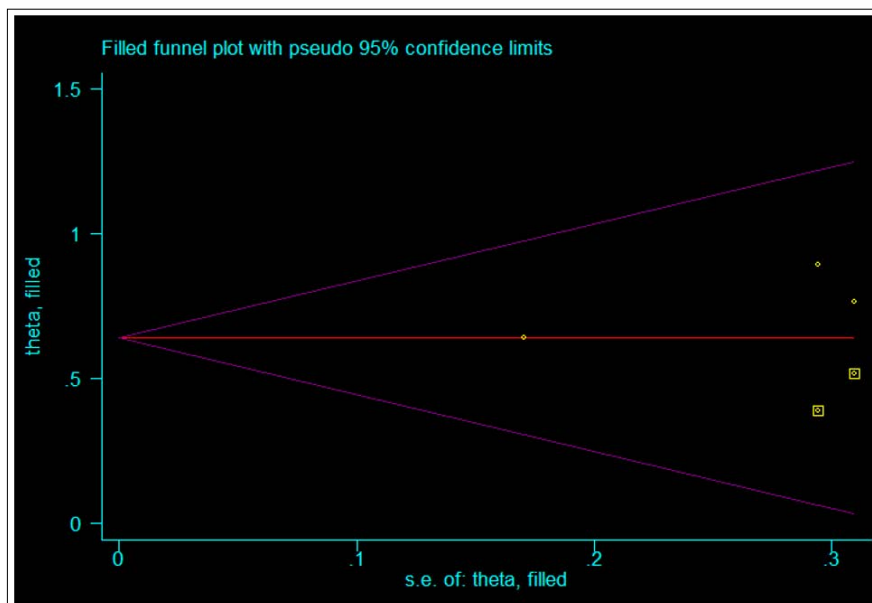


Figure 12: Filled funnel plot with pseudo 95% confidence limits for the log odds ratio of effect of TB contact history on developing MDR-TB, the circular dots indicate the observed studies and the square dots indicate the missing studies imputed by the trim-and-fill method (based on the linear estimator) Ethiopia, 2021

Note: Theta is log odds ratio and s.e. of theta is standard error of Log odds ratio

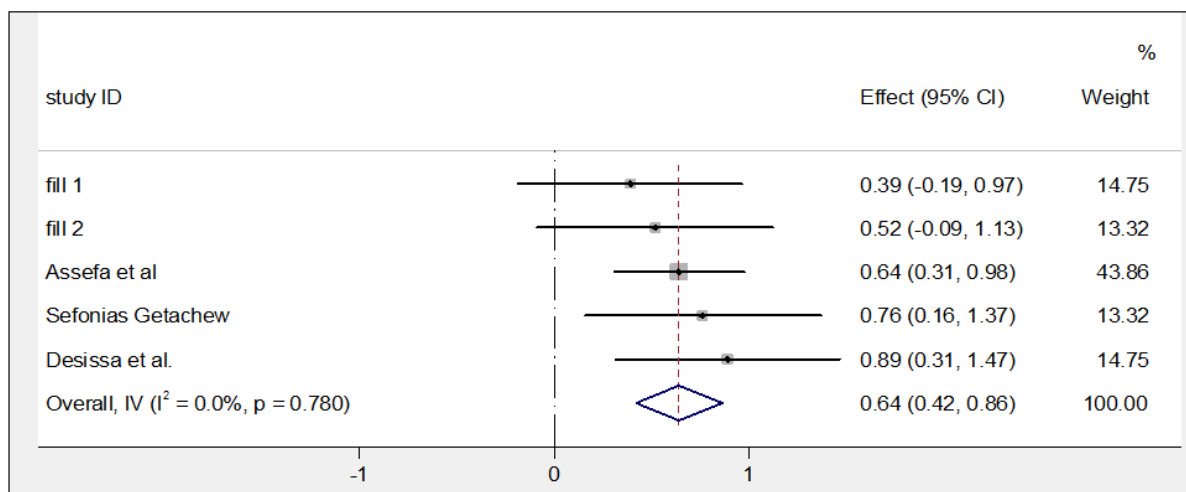


Figure 13: A forest plots of studies for the pooled log odds ratio of the effect of TB-contact History on MDR-TB following trim and fill analysis, Ethiopia, 2021

Effects of Contac History with a known MDR-TB patient on MDR-TB

Four studies (all case-control), giving total sample size of 849, were found eligible for meta-analysis to measure the effect of contact History with a known MDR-TB patient on MDR-TB (Table 5) [33,37,38,41].

Table 5: The Characteristics of Studies included for the meta-analysis of the effect of having Contact History with Known MDR-TB case on MDR-TB, Ethiopia, 2021

Study Author	year Published	place conducted	Study design	MDR-TB with contact Hx		MDR-TB with no contact Hx		Sample size
				Yes	No	Yes	No	
Sefonias Getachew	2012	Addis Ababa	case_control	13	11	56	127	207
Mulu, W et al.	2015	Amhara region	case_control	44	22	109	131	306
Gobena, D et al.	2018	Jimma	case_control	35	15	24	58	132
Fikre A et al.	2019	Southern Ethiopia	case_control	19	11	83	91	204
Total				111	59	272	407	849

The pooled analysis of the effect of contact history to MDR-TB case on the risk of developing MDR-TB was statistically significant. The forest plot below showed that individuals who had contact history with MDR-TB patient were 2.85 times more at risk of developing MDR-TB compared to those who did not have contact history with a known MDR-TB patient (Pooled OR=2.85, 95%CI: 1.82-4.44). Regarding the heterogeneity of the studies, the variance between studies (Tau2 =0.07), test for significance difference between the studies (chi2 =4.38, p=0.22) and the percentage variation is low (I2=32%) (Figure 14).

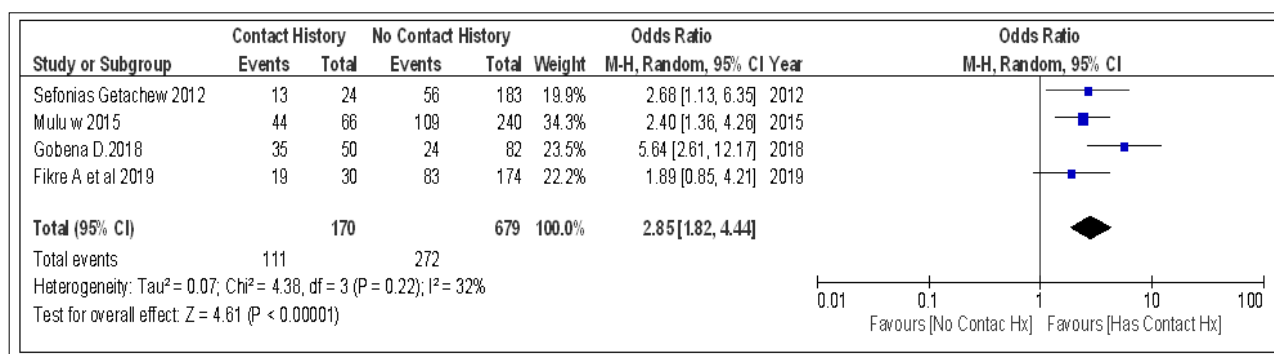


Figure 14: Forest plot of comparison of effect of having Contact History Vs without contact History to a known MDR-TB patient on MDR-TB, Ethiopia, 2021

The funnel plot assessment of publication bias showed a fairly symmetrical distribution of the individual studies' effect size (log OR) around the pooled log odds ratio which is an indication of absence of publication bias and no need for trim-and-fill analysis (Figure 15).

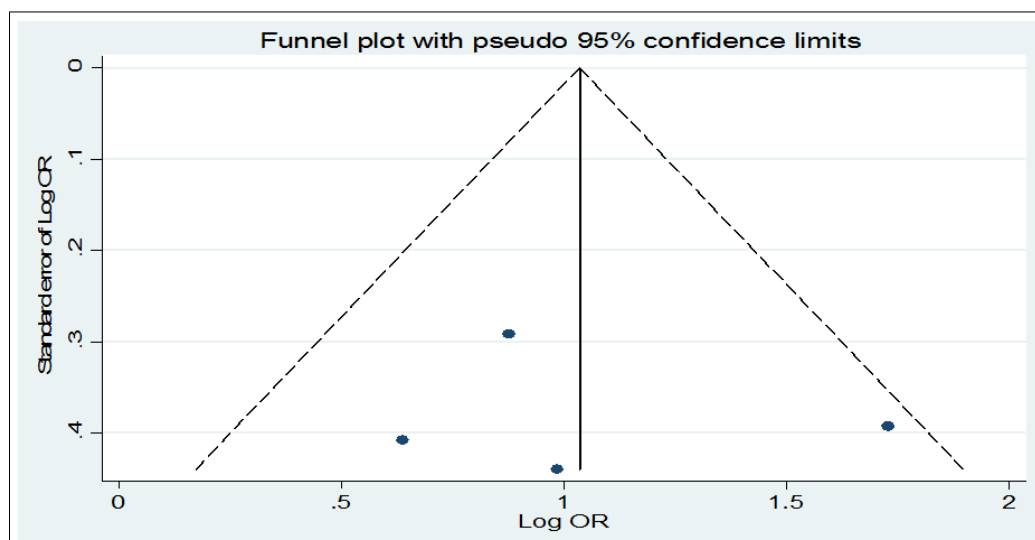


Figure 15: funnel plots with pseudo 95% confidence interval of studies in the pooled analysis of the effect of MDR-TB contact history on the development of MDR-TB, Ethiopia, 2021

Discussion

This Meta analysis was done on the most commonly reported clinical risk factors of MDR such as HIV infection, previous anti-TB treatment history, contact history with known TB patient and contact history with known MDR-TB patient. In the analysis HIV infection has no statistically significant effect on the acquisition of MDR-TB both before (pooled OR=1.50, 95%CI: 0.73-3.10) and after adjusting for publication bias (Adj.pooled log OR= -0.2, 95%CI: -0.40, 0.00). This finding is in line with the meta-analysis conducted in Sub-Saharan Africa countries that reported HIV is not a risk factor for drug resistance TB, with the overall risk ratio (RR) of 1.1 (95% CI, 0.92 to 1.23) [23]. However, it contradicts with the meta-analysis findings that included studies done globally and reported HIV is a risk factor for developing MDR-TB, with the pooled odds ratio of 1.24 (95% CI 1.04 to 1.43). Though the analysis by Mesfin et al reported statistical significance association of HIV and MDR-TB, it was too marginal as noticed from the confidence interval. Moreover, most (18 out of 24) of the studies included in the analysis were cross-sectional, as a result might tends to report significant association more likely than other study designs [32]. This is what observed in this meta-analysis that in the sub-group analysis by study type the pooled odds ratio for cross-sectional studies showed statistically significant association between HIV and MDR-TB (Pooled OR=3.79, 95%CI: 1.61-8.92). Moreover, there was inconsistency in the studies report about the association between HIV and MDR-TB. Four case-control studies reported reduced risk, while three case-control studies reported increased risk of developing MDR-TB among HIV positives [26,27,36,37,39,40]. However, all (five) cross-sectional studies included in the analysis were reported increased risk of developing MDR-TB among HIV positives [14,42,43,46,48].

In this meta-analysis it was observed that a previous anti-TB treatment is a risk factor for developing MDR-TB both before (pooled OR=7.63, 95%CI: 3.76, 15.5) and after (Adj. pooled log OR= 1.07, 95%CI: 0.85, 1.29) adjusting for report bias. Among eleven studies included in the analysis (5 case-controls and 6 cross-sectional), ten (except Nigus et al. 2014) reported statistically significant association of previous anti-TB treatment and MDR-TB [19,26,27,33,35,36,41-48]. The finding of this meta-analysis was supported by the meta-analysis done in sub-Saharan Africa that reported the risk of developing MDR-TB in previously anti-TB treated cases were more than fivefold higher than new cases (overall RR = 5.7; 95% CI, 3.61 to 8.96) [23].

Regarding the effect of contact history with a known TB case on the risk of developing MDR-TB, the analysis showed that it is a risk factor for acquisition of MDR-TB with unadjusted pooled OR=1.91, 95% CI: 1.52, 2.39 and adjusted pooled Log OR=0.64, 95%CI: 0.42, 0.86). In this analysis one study, though not significant, reported a reduced risk of developing MDR-TB among those with history of contact to known TB case (AOR=0.65, 95%CI: 0.13-3.26), the rest two studies, however reported history of contact to known TB case is a risk factor for developing MDR-TB, (AOR=1.96, 95%CI:1.13–3.38) and (AOR= 2.1, 95%CI: 1.04–4.43) [34,35,37]. The publication bias adjustment was indicative of two articles that need to be published were missed and subsequently filled. Following the filled analysis the heterogeneity was found not significant ($I^2=0.0\%$, $P=0.78$) unlike it was found in the analysis of effects of HIV and pervious anti-TB treatment. This is in line with the article entitled the trim-and-fill method for publication bias that for most meta-analyses with binary outcomes, their heterogeneity remained non-significant after the trim-and-fill method, while around 20% meta-analyses remained significantly heterogeneous [49].

Contact history with known MDR-TB patient was found a risk factor for acquisition of MDR-TB (Pooled OR=2.85, 95%CI: 1.82-4.44). All of the four case-control studies included in the analysis reported increased risk of developing MDR-TB among those who had contact history with known MDR-TB patient [33,37,38,47].

Conclusion and Recommendation

In conclusion in this meta-analysis, it was tried to look at the effects of clinical risk factors including HIV, previous anti-TB treatment history, contact history with known TB case and contact history with known MDR-TB case on the risk of developing MDR-TB. It was found that except HIV sero-status the other clinical risk factors such as previous anti-TB treatment history, contact history with known TB case and contact history with known MDR-TB case were risk factor for acquisition of MDR-TB. The trim-and-fill analysis done following funnel plot assessment for three clinical factors such as HIV sero-status, previous anti-TB treatment history and contact history with known TB case, showed that the heterogeneity due to publication bias became significant before and after the trim and fill analysis except for the factor contact history with known TB case.

We recommend that a strict infection prevention practice should be followed; primarily in preparation of the pulmonary TB and MDR-TB patients' isolation rooms and subsequently isolation of such patients in clinical setups to the level of not only to reduce rather to avoid contact with them.

Anti-TB drug management should be strictly practiced by both care providers and TB patients to minimize the development of drug resistance following inappropriate use since most cases of MDR-TB are among those with previous anti-TB treatment history.

A health regulation and legal frame work should be designed, specific to the practice of anti-TB drug management and use that involves legal punishment for incorrect practice both by the care provider and the TB patient in the DOTS program since the worry is not for having a single case of TB rather this single case might harbor resistant strain and through contact disseminate the strain hence it is about protecting the public.

Furthermore, reviewers need to synthesized evidence with more reliable method such as meta-regression to account for confounding factors which might contribute for the observed substantial heterogeneity of studies in this analysis.

Declarations

Ethics approval and consent to participate

Ethical clearance was obtained from ethical review committee of Bahir Dar University, College of Medicine and Health Sciences, School of Public Health and Department of Biostatistics and Epidemiology. Consent to participate is not applicable since this analysis did not take data from individual person.

Consent for publication

Consent for publication is not applicable. This study did not take individual person's detail such as name, images, or videos.

Availability of data and material

The data used for the meta-analysis is presented with tables and included in the manuscripts

Competing interests

The authors have no any competing interests exists as defined by

PLOS, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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Authors' contributions

G.H, conceptualization, methodology, formal analysis and writing-original draft. G.T, A.G and A.M. Data curation, Investigation and writing-review and editing.

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