ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCE

SCHOOL OF PUBLIC HEALTH

ASSESSMENT OF THE ASSOCIATION BETWEEN HIV/AIDS AND MULTI DRUG RESISTANCE TUBERCULOSIS:

A SYSTEMIC REVIEW WITH META-ANALYSIS

BY: ASMAMAW MOGES (BSc, PH)

ADVISOR: DAMEN HAILEMARIAM (PROFESSOR)

A RESEARCH THESIS SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES OF ADDIS ABABA UNIVERSITY, SCHOOL OF PUBLIC HEALTH, COLLEGE OF HEALTH SCIENCES, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN EPIDEMIOLOGY (MPH)

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Asmamaw Moges Mesfin (BSc, PH)

Approved by Examining board

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Chairman, school of Public Health Academic Commission	Signature
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Advisor	Signature
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External Examiner	Signature
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Internal Examiner	Signature

June, 2012

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ABBREVIATIONS/ ACRONYMS'

AFB; Acid Fast Bacilli

AOR; Adjusted Odds Ratio

AIDS; Acquired Immune Deficiency Syndrome

ART; Antiretroviral Therapy

CI; Confidence Interval

CDC; Communicable Disease Control

DRTB; Drug Resistance Tuberculosis

DST; Drug Sensitivity Test

EPTB; Extra Pulmonary Tuberculosis

HIV; Human Immunodeficiency Virus

INH; Isoniazid

MDR-TB; Multi-Drug Resistance Tuberculosis

OR; Odds Ratio

PLWHA; People Living With HIV/AIDS

PTB; Pulmonary Tuberculosis

RMP; Refampicin

STM; Streptomycin

UK; Unite kingdom

WHO; World Health Organization

XDR-TB; Extensive Drug Resistance Tuberculosis

ABSTRACT

Back ground:

Human immunodeficiency virus, multi-drug resistant tuberculosis and extensive drug resistant tuberculosis are emerging as major challenges facing tuberculosis control programs worldwide (especially in Asia and Africa). The challenge is not only from a public health point of view but also in the context of global economy, especially in the absence of treatment for multi-drug resistant tuberculosis at national-level programs in developing countries. The association between multi-drug resistant tuberculosis and Human Immunodeficiency Virus infection has not yet been fully investigated and the results of the studies so far conducted were not consistent.

Objective: The aim of this study was to summarize the evidence on the association between multi-drug resistant tuberculosis and HIV infection through a systematic review of existing literature.

Methods: Literature based systemic review of observational studies was conducted. Original studies providing Mycobacterium tuberculosis resistance data stratified by Human Immunodeficiency Virus status were identified using data bases such as MEDLINE/PUBMED, Google Scholar and HINARI. The descriptions of original studies were made using frequency and forest plot. Publication bias was assessed using Funnel plot graphically and Egger weighted and Begg rank regression tests statistically. Heterogeneity across studies was checked using Cochrane Q test statistic and I^2. Pool risk estimates of multi-drug resistance tuberculosis and sub-grouping analysis were computed to analyze associations with Human Immunodeficiency Virus status.

Results: Random effects meta-analysis of all the 24 observational studies showed that Human Immunodeficiency Virus infection was associated with an increased risk of multi-drug resistant tuberculosis (summery odds ratio 1.24; 95%, 1.04 – 1.43). Subgroup analyses showed that effect estimates were higher for primary multi-drug resistance tuberculosis and in population based studies.

Conclusions: Human Immunodeficiency Virus infection is positively and significantly associated with an increased risk of multi-drug resistant tuberculosis regardless of study base and multi-drug resistant tuberculosis type. There should be strong collaboration between Human Immunodeficiency Virus and tuberculosis control programs.

1. INTRODUCTION

1.1. Back ground:

Tuberculosis (TB) is a chronic infectious disease mainly caused by *mycobacterium tuberculosis* (MTB). Occasionally caused by other organisms of the Mycobacterium tuberculosis complex- *M. bovis, M. africanum, M. canetti* and rarely, *M. microti* (1). TB has been causing great suffering to human beings throughout recorded history. Even today, more than a century after the discovery of the infectious agent and, five decades after introducing effective chemotherapy and more than two decades after introduction of DOTS control strategy, tuberculosis still remains a major cause of morbidity and mortality worldwide (2). One-third of the world's population is estimated to be infected with mycobacterium tuberculosis (2). In 2010, there were 8.8 million (range, 8.5–9.2 million) incident cases of TB, 1.1 million (range, 0.9–1.2 million) deaths from TB among HIV-negative people and an additional 0.35 million (range, 0.32–0.39 million) deaths from HIV-associated TB (3). Human immunodeficiency virus (HIV), multi-drug resistant TB (MDR-TB), and extensive drug resistant tuberculosis (XDR-TB) is jeopardizing (risk of failure) TB control program worldwide (4).

Multi-drug resistance tuberculosis (MDR-TB) is defined as tuberculosis that is resistant at least to isoniazid (INH) and rifampicin (RMP), the two most powerful first-line anti-TB drugs. World Health Organization (WHO) has documented that MDR-TB is emerging as a major challenge for tuberculosis control programs and is becoming extensively widespread today throughout the world even in high-income countries with low TB incidence. It is a challenge not only from a public health point of view but also in the context of global economy, especially in the absence of treatment for MDR-TB at national-level programs in developing countries (4).

According to data, in 2010, about 650 000 cases of MDR-TB (which account for 5% of all newly diagnosed TB patients) and more than 150,000 MDR-TB deaths are estimated to occur worldwide each year with case fatality rate of 30 per 100 individuals (4). The proportion of MDR-TB reported globally ranges from 0% to 28.3% and 0% to 61.6% among new TB cases and among previously treated TB cases respectively (5). India, China and the Russian Federation were estimated to have the highest number of MDR-TB cases. China and India are estimated to carry 50% of the global burden, with the Russian Federation carrying a further 7%. Twenty

seven high priority countries (15 in the European Region) account for 86% of MDR TB in the world (6). However, the magnitude of MDR-TB is not known precisely because of the lack of prevalence information from all countries. Most sub–Saharan African countries have been unable to carry out the necessary laboratory investigations because of the absence of appropriate equipment to identify the M. tuberculosis strains resistant to the four drugs used in the first-line treatment (7).

The Human Immunodeficiency Virus (HIV) pandemic is also one of the greatest challenges facing tuberculosis (TB) control programs. Immune suppression increases the risk of reactivation of latent TB infection and rapid progression to active TB disease (8). Taking everything into account, an estimated 12% of new TB cases are attributable to HIV co-infection and 400.00 of the 1.7 million TB deaths in 2010 were attributed to HIV infection; but in the African Region this proportion has been much higher (9). The risk of death in co-infected patients is twice that of HIV–infected individuals without TB, even when CD4+ cell count and antiretroviral therapy are taken into account (10).

People living with HIV are at a higher risk of developing multi-drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis associated with increased mortality, and greatly reduced survival time (10). HIV and MDR-TB are equally balanced deadlier combinations (11). More than 50% of HIV-infected MDR-TB patients in Peru died within two months of diagnosis. Other studies with longer follow up observed death rates ranging from 72 to 89% (12). A study in the United Kingdom (UK) estimated that MDR-TB patients who are immune-compromised are nine times more likely to die than those not immune-compromised (13).

1.2. Rationale of the Study:

Even if the impact of HIV infection on MDR-TB is of great public health importance, the relationship between the two infections is not yet clearly understood. Findings from different studies on associations of HIV co infection and drug resistance among patients with TB have been contradictory (discordant). Some institution based studies found strongly increased risks for multidrug resistant TB (MDR TB) among patients co infected with TB and HIV(14-17), whereas other studies found no increased risk (it remains less clear in community based studies) (18-20). The question of whether HIV co-infection places a person at increased risk for drug resistance

remains largely unanswered. Knowing of the real association between MDR-TB and HIV is critical for harmonizing tuberculosis and HIV/AIDS control programs locally (in Ethiopia) as well as globally and for policy makers at different levels.

Therefore this study was aimed at summarizing and critically appraising institution and community based observational studies throughout Africa and in the world in order to determine the relationship between MDR-TB and HIV-infections.

2. LITERATURE REVIEW

2.1. Over view of Drug Resistance Tuberculosis:

Tuberculosis, despite major advances in our understanding of communicable diseases, remains the most important cause of morbidity and mortality in the world today. One-third of world's population is estimated to be infected with mycobacterium tuberculosis. More than 95% of tuberculosis cases occur in the developing world, where tuberculosis accounts for over 25% of all preventable adult deaths (2). Several key issues threaten global control of TB. Firstly, HIV/TB co-infection, particularly in Africa, is a growing challenge. TB is the leading cause of death for people with HIV, and TB control is significantly impeded in areas with high HIV prevalence. Secondly, drug-resistant forms of TB, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDRTB), are more difficult and expensive to treat, leading to greater TB-related mortality (4). TB diagnosis is more difficult in people living with HIV infection and initiation of HIV treatment can paradoxically worsen TB by restoring immune function. Tuberculosis is the leading cause of death among HIV infected patients in the developing world (9).

Drug resistance was first recognized during 1940s. But, as a major problem it was recognized in 1992, when 12% of the tuberculosis patients in New York City were found to have MDR tuberculosis. MDR tuberculosis spread around the world because of the lack of or inadequacy of tuberculosis control programs, insufficient resources, and inadequate protective measures against infection, as well as delayed diagnosis of tuberculosis (4).

Multi-drug resistance tuberculosis develops during the course treatment of TB when it is interrupted and the level of drug in the body are insufficient to kill 100% of bacteria (acquired MDR-TB) and direct transmission of an MDR-TB strain (primary MDR-TB). Acquisition of MDR-TB can arise from inappropriate use of anti-TB drugs during the treatment course of TB patients with drug susceptible strains (medical error and poor patient adherence to treatment) as well from poor TB control programs (21).

MDR-TB is of great concern because standard short course chemotherapy, based on first-line drugs, was inadequate to treat patients with MDR-TB and the treatment of patients with MDR-TB relies on drugs that are less potent, that need to be administered for a much longer time (18-

24 months) and are substantially more toxic than those used to treat TB caused by drug-susceptible strains. Furthermore, the cost of a second-line drug regimen is much higher: up to thousands of dollars compared with the cost of about $US 20 per patient for the standard 6-month short-course, first-line chemotherapy regimen (WHO category 1). In addition, the treatment of patients with MDR-TB needs a period of hospitalization to manage their toxic reactions and other complications (21).

2.2. Association of Multi-Drug Resistance Tuberculosis and HIV/AIDS:

Literature shows that factors such as male sex, young age group (22), TB known contact, alcoholism, socioeconomic status (22, 23) and co-morbidities, such as HIV infection (23) and diabetes mellitus (24) were to be associated with the increase prevalence of MDR-TB.

The issue of HIV infection being a risk factor for MDR-TB has been discussed for several years. The controversy started with the communicable disease control (CDC) publication on the MDR-TB outbreak among HIV-infected subjects in New York and Miami (4).

Infection with HIV could influence tuberculosis drug resistance through behavioral/environmental or biological mechanisms. For example, certain HIV-positive population groups, such as injecting drug users, may have behavioral risk factors that make them less likely to adhere to tuberculosis treatment, resulting in the development of resistant strains (acquired resistance), which are then transmitted within that community (resulting in initial resistance). Since immune compromised patients are more likely to develop disease and to do so more rapidly than immune competent patients, extensive transmission of drug resistant strains may occur (25). HIV-positive patients might also be more likely to visit frequently settings in which they could be exposed to drug-resistant strains of tuberculosis, such as hospitals, and could be more susceptible to drug-resistant tuberculosis strains that are possibly less virulent (26). Furthermore, HIV infection may impair the absorption of some anti tuberculosis drugs, contributing to the development of resistance (27). Drug interactions and adverse reactions may also be more likely among HIV co-infected patients and could lead to treatment interruptions; this will again promote the development of resistance (27).

Even though the epidemiological impact of HIV on the epidemic of drug resistance TB is not well known, several factors are proposed. HIV infected TB cases are more likely to be smear negative, and delayed diagnosis of drug resistance as well as unavailability of treatment have led to high death rates in people living with HIV. Both of these factors may suggest a lower rate of transmission. However, HIV infected cases progress rapidly to disease, and in settings where MDR-TB is prevalent, either in the general population, or in the local population such as a hospital or prison, this may lead to rapid development of a pool of drug resistant TB patients, or an outbreak. Furthermore, people living with HIV may also be more likely to be exposed to MDR-TB patients, due either to increased hospitalizations in settings with poor infection control or association with peers who may have MDR-TB, including in penitentiary settings (5).

A case control study, which was conducted in four European countries to assess risk factors for multi-drug resistance tuberculosis, identified immigration, aging, HIV infection, population mobility and drug use as likely risk factor for MDR-TB. In this study significant differences were not found by HIV status (HIV sero-negative with OR of 1.17, 95% CI 0.8–1.8 and unknown with OR of 0.65, 95% CI 0.4–1.1) (28). However, a prospective a study in Peru, after excluding patients with history of prior episodes of TB or TB prophylaxis, showed that MDR-TB was seen in 18 (43%) of 44 isolates from HIV-infected persons versus 24 (3%) of 814 HIV-negative controls ($p < 0.001$) (16). Another retrospective case control study in South Africa on clinical predictors of MDR-TB and XDR-TB has identified HIV as an independent risk factor for XDR-TB (aOR 8.2, 95% CI 1.3-52.6) but not for MDR-TB (aOR 1.4, 95% CI 0.5-4.0) (29). More over a case control study from Burkina Faso, West Africa, to examine the risk factors for multidrug resistance tuberculosis (MDR) among patients with pulmonary tuberculosis (TB) showed that HIV infection was not a risk factor associated with MDRTB with adjusted odds ratio of 1.434 (0.218–9.446) (21).

No association between HIV/AIDS and MDR-TB was documented from cross-sectional studies in Samara Region, Russia, showing that being male, having history of TB previous or current treatment for more than four weeks and history of imprisonment remained as highly significant factor for single drug resistance and MDR-TB. HIV positivity was not associated with drug resistance. But, as recreational drug use, the main route of HIV infection is strongly associated with MDR-TB in new cases; HIV co infection is likely to become increasingly significant (30).

The same study design from Kampala- Uganda and Georgia found no association between any resistance to anti TB drug and HIV infection with odd ratio of 0.7 (0.4–1.3) and 1.40 (0.47—4.17) respectively. But, the number of MDR cases was small and thus limited the precision of this estimate (31, 32).

According to recent data (WHO 2010 report), HIV-positive TB patients in three Eastern European countries (Estonia, Latvia and the Republic of Moldova) appear to be more at risk of harboring MDR-TB strains. Furthermore, in Lithuania – where drug resistance data could not be disaggregated by HIV-negative and unknown HIV status, HIV-positive TB patients had a 8.4 (95% CI: 2.7– 28.2) times higher odds of harboring MDR-TB strains than TB patients for whom HIV status was unknown. This finding showed that a possible association of the two epidemics. In addition, preliminary results of a survey conducted in Mozambique in 2007 have also found a significant association (5)

A study conducted in Ukraine, with the objective of exploring the association between the epidemics of human immunodeficiency virus (HIV) and multidrug-resistant TB (MDR-TB), showed that rates of MDR-TB and resistance to any first-line anti-tuberculosis drugs to be higher in PLWH with RRs of 1.3 (95% CI 1.1–1.5) and 1.1 (95% CI 1.0–1.3), respectively. In this study the association between MDR-TB and HIV infection was found to be statistically significant among new cases (RR 1.5, 95% CI 1.1–2.0), but not among those with a history of previous treatment (RR 1.1, 95% CI 0.9–1.5). The multivariate analysis also showed that HIV-positive status was strongly increased the risk of MDR-TB (HIV-positive status OR 1.7, 95%CI 1.3–2.3) (10). A case-control study and another eight years surveillance study in France showed significant positive association between HIV and primary MDR-TB with adjusted odd ratio of (2.02, 95% confidence interval 1.04–3.95) and (3.3, 95% CI 1.5 to 7.3) respectively (33, 34).

A cross-sectional prevalence study of MDR-tuberculosis at a VCT Center in Haiti indicated that; MDR tuberculosis prevalence of 6% and 20% with recurrent tuberculosis. In patients with primary disease,10% of HIV-infected patients had MDR tuberculosis compared with 3% of HIV-negative patients (35). A systematic review of twenty nine papers in Europe on risk factors for MDR-TB showed that, being HIV positive was significant risk factor for MDR-TB (OR 3.52, 95% CI 2.48 - 5.01). But the included articles were five in number and there were selection bias in favor of HIV infected individuals among cases studied for sensitivity of (23).

In summary, the available evidence on the association of multi-drug resistance tuberculosis and HIV/ AIDS was controversial and there was no credible documentation on whether HIV/AIDS was an independent predictor of multi- drug resistance tuberculosis or not. This study tried to summarize the available evidence on the association of HIV/AIDS and multi-drug resistance tuberculosis.

3. RESEARCH QUESTION

The research question of this study was;

- Is HIV/AIDS an independent risk factor for multi-drug resistance tuberculosis?

4. OBJECTIVE

4.1. General Objective:

To summarize the evidence of the association between HIV/AIDS and multi-drug resistance tuberculosis through a systemic review and meta-analysis of studies during the period of October 1, 2011 to april1, 2012.

4.2. Specific Objectives:

1. To summarize the evidence on the association between HIV infection and multi-drug resistant tuberculosis; and
2. To estimate the effect of HIV infection on multi-drug resistance tuberculosis.

5. METHODS AND MATERIALS

5.1. Study design and data source:

A systematic review with meta-analysis of published and unpublished reports dealing with risk factors (HIV infection) for MDR-TB in Africa and at global level was carried out. Studies were identified through a computerized search of the following databases: Pub Med/Medline, HINARI and Google Scholar. The search terms drug resistance, multidrug resistance, MDR-TB, HIV/AIDS and any of the following—risk factors, epidemiologic/clinical determinants, predictors, correlates, surveillance, and surveys - were used as a combination of free text and thesaurus terms in different variations. The International Journal of Tuberculosis and Lung Disease was selected as the key journal for hand searching. Search was also made for reference lists of identified original articles and reviews for other relevant articles. The search was performed from October 1 to April 10, 2012 and all articles on human subject research prior to the search date were considered.

5.2. Study Selection:

Review was made on observational studies (cross-sectional, surveillance/survey, case-control and cohort studies) which reported on the association of HIV infection and MDR-TB. Articles were included, if they presented results based on drug susceptibility to rifampin and isonized of mycobacterium tuberculosis and stratified by HIV status (independent of study design and without restriction of publication date). Reports of original studies, unpublished master's thesis and PhD dissertations which were written in English language also considered while comments, editorials and reviews were excluded. Studies were excluded from the analysis for any of the following reasons: articles focused only on extra-pulmonary tuberculosis; those dealing with a mycobacterium other than tuberculosis; those that did not consider HIV as risk factors (independent variable); studies that do not provide effect estimates in odds ratios, rate ratios, or risk ratios, or did not allow the computation of such; studies among children <14 years; meta-analyses or systematic reviews; duplicate publication of the same study; and articles available only in abstract form. Articles with sample size of less than 50 were also excluded. Studies that did not fit for quantitative analysis were reserved for narrative analysis. The selection of articles for review was done in 3 stages: titles alone, then abstracts, and then full-text articles.

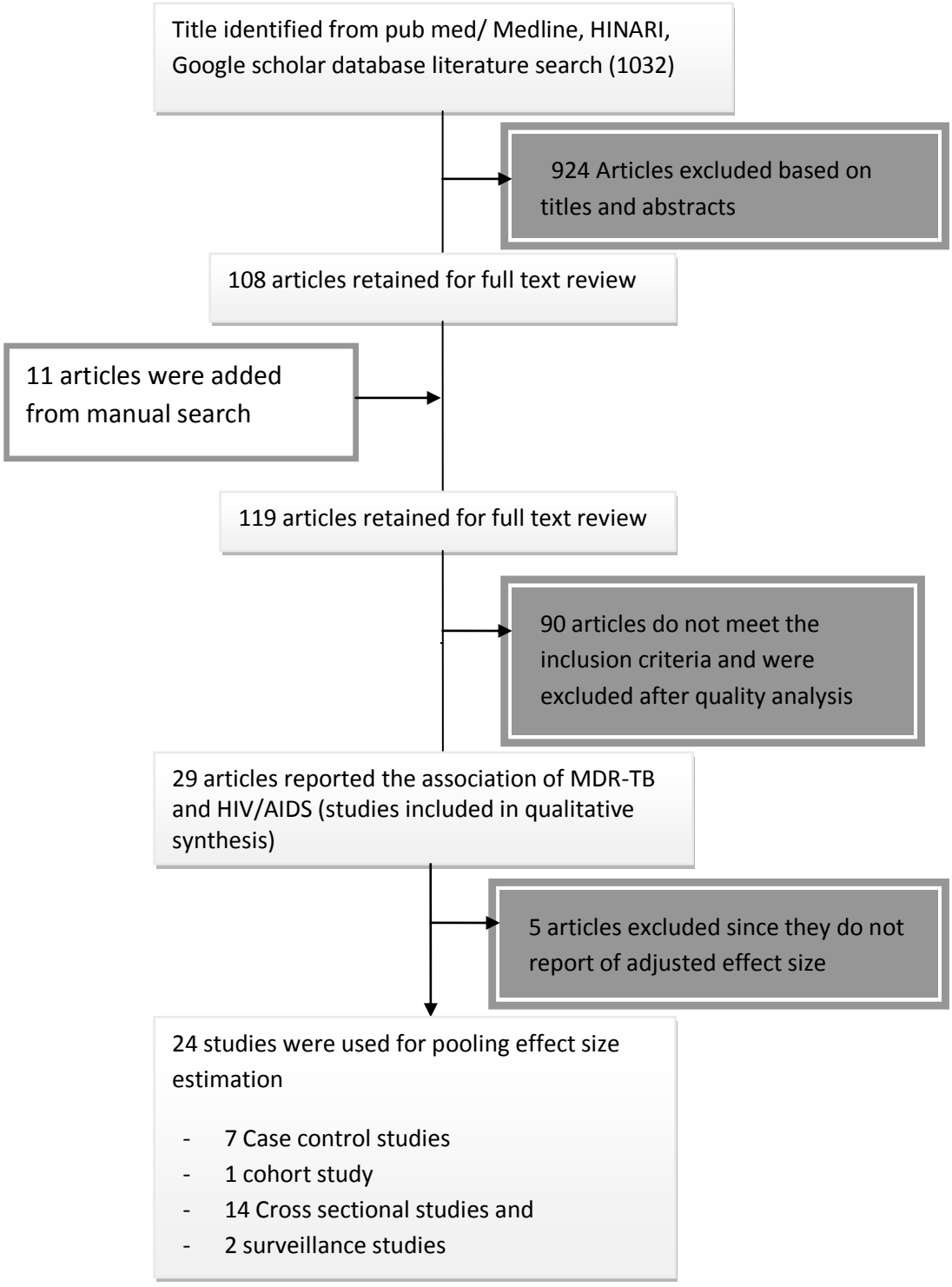

Figure 1: Flow chart diagram describing selection of studies for a systematic review (identification, screening, eligible and included studies). Articles may have been excluded for more than one reason.

5.3. Methodological quality assessment:

Method of confirmation of TB, MDR-TB and HIV status, sample size, describing MDR-TB by HIV status, use of appropriate statistical measurement to assess the association between MDR-TB and HIV infection and assessment and adjustment of potential confounders (demographic, socio-economic and previous TB treatment and known contact with TB patient related variables) were noted as quality of indicators. Reporting of response rate, lost to follow up and appraisal of external validity of study result were also considered as study quality indicators. Each question was answered with a yes, no or don't know response option.

All assessments were entered into preformatted extraction forms. Studies were assessed for quality and studies with medium (fulfilling 50% of quality assessment parameter) and high quality were included for analysis. High quality studies were: studies that reported outcomes on at least 50 patients; cohort studies with lost follow up of less than 20%, case control studies (matched or unmatched), cross-sectional studies and surveillances whose response rate was greater than 80%; those that reported basic demographic data, clear stratification for unknown and HIV negative individuals and adjustment for covariates like demographic, socio-economic and previous TB treatment and known contact with TB patient related variables.

5.4. Data Extraction:

The selected studies were reviewed by using pretested and standardized abstraction form to abstract data about title; authors, year of publication, country, study design, study site, study base (population-based or hospital-based), sample size, data collection procedure, TB form (pulmonary, extra pulmonary), type of MDR-TB (primary, acquired TB), Human Immunodeficiency Virus (HIV)status, adjustment and stratification factors, response rates, measure of association like OR/ RR with its confidence interval (CI), P-values, proportion of exposed and who developed the disease for different categories and standard deviation (SD) or standard error (SE).

5.5. Data Synthesis:

In accordance with the World Health Organization's definitions for tuberculosis control (36), any drug resistance is defined as resistance to one or more first-line drugs. 'Mono resistance' is

defined as resistance to only one of the five first-line drugs (INH, RMP, STM, EMB, and PZA). MDR-TB is defined as M. tuberculosis strains that are resistant to at least INH and RMP. Primary or initial resistance, (resistance among new cases), is defined as patients with TB resistant to one or more anti-TB drugs, but who had never been previously treated for TB or had treatment less than one month. 'Secondary resistance' (resistance among previously treated cases) is defined as patients diagnosed with TB who started anti-TB treatment and subsequently acquired resistance to one or more of the drugs used during the treatment.

5.6. Statistical Analysis:

Epi-info version 3.5.1 and STATA version 11.0 using metan command (STATA Corporation, College Station, Texas) software were used for data entry and analysis respectively. The descriptions of original studies were assessed by using frequency and forest plot. The overall effect (pooled effect size) of HIV infection on MD-TB was carried out by using the Der Simonian-Laird random-effects meta-analysis (random effects model) and measured by odds ratio with 95% confidence intervals [95%CI]. Sub-group analyses were performed according to study base (population based or hospital based), study design (cross-sectional and surveillance and case-control), type of multi- drug resistance tuberculosis (primary or secondary), adjustment for potential confounders (demographic, socio-economic and previous tuberculosis treatment and known contact) and based on selection of controls (hospital and discharge record based vs. population based) for case-control studies.

5.7. Exploration of Publication bias and Heterogeneity:

Publication bias was assessed using Funnel plot through the displaying of individual study OR with 95% confidence intervals (CIs). The Begg rank correlation and Egger weighted regression test methods were also used to statistically assess publication bias ($P<0.05$ was consider as indicative of statistically significant publication bias). Cumulative meta-analysis also used to see the effect of each study and less precise studies on the pooled estimates.

Statistical heterogeneity was assessed with Cochran's Q test, which tests if the amount of between study heterogeneity is greater than due to chance (39) and I2 statistic the magnitude of statistical heterogeneity that can be expected by partitioning out the chance heterogeneity (40).

The I^2 statistic is a measure of the proportion of variability (inconsistency) between studies that is due to chance as opposed to the actual difference between study populations. Therefore, the presence of statistical heterogeneity was tested using Cochran's Q ($P<0.10$ was considered indicative of statistically significant heterogeneity) test and the recently developed measures magnitude of statistical heterogeneity between trials using I2 (values of 25%, 50% and 75% are considered to represent low, medium and high heterogeneity respectively).

5.8. Dissemination of Findings:

Finding of this study will be disseminated to concerned bodies, like AAU school of public health and health institutions and organizations including ministry of health. In addition, findings will be presented in seminars, conferences, and symposium as well as published in journal to access others.

5.9. Ethical Clearance:

Ethical clearance was obtained from review ethics committee of school of public health, Addis Ababa University.

6. RESULTS

6.1. Identified Studies:

A total of 1032 original articles were identified from the initial PubMed, HINARI and Google Scholar search on MDR-TB risk factors and 11 additional papers were identified from a manual search of International Journal of Tuberculosis and Lung Disease. Of these, 924 were excluded after screened by titles and abstracts, those that were duplicated studies, and those that were case reports, reviews, or studies of mono drug resistance tuberculosis and extensive drug resistance tuberculosis. Of the remaining 119 articles, 90 studies were excluded because they were: studies of MDR-TB other than M. tuberculosis (9); studies of MDR-TB treatment outcome (12); they were systemic review and meta-analysis (3); they did not consider HIV/AIDS as independent variable (22), and access could not be gained to the full article or data (8); were on children (5); were dealt only on extra pulmonary tuberculosis (6); their sample size were less than 50 (6), and did not give a quantitative effect estimate (8). Further exclusion of studies that did not adjust for covariates (9) was also made. Finally 24 articles were used for the meta-analysis. See figure 1 for the flow of the diagram for study selection.

6.2. Characteristics of Included Studies:

Seven of the 24 studies selected for meta-analysis were case control studies (21, 28, 29, 33, 39-41), one study was prospective cohort study (42) and the rest 16 were cross sectional studies and surveillance (10, 15, 32, 34, 35, 43-52). Twenty two of them were institution based (15, 21, 28, 29, 32-35, 39, 41, 43-45, 47-53) or based on discharge records and two were population based (40, 46). The resulting 24 studies addressing the association of HIV and MDR-TB, which had study populations varying from 172 in New York City (50) to 55,571 in France (34), were carried out between 1990 and 2011. All studies were reported in English.

The 24 retrieved studies represented 16 countries in 6 regions (South/Southeast Asia, Sub-Saharan Africa, Western Europe, Eastern Europe, Latin America, and North America) and were set in South Africa (3), Mozambique (1), Burkina Faso (1), Ethiopia (1), Uganda (1), Haiti (1), Georgia (1), Ukraine (1), Estonia (1), Brazil (1), England and Wales (1), France (2), Italy (1), nether land (1), four European countries (1), Thailand (2) and USA (4). General characteristics and description of the studies selected for meta-analysis are outlined in table 1.

Table 1: Summary of the 24 observational studies assessing the association between HIV/AIDS and multi-drug resistance tuberculosis included in the meta-analysis.

First author, year, country	Design	Sample size	MDR-type	Number HIV+	MDR-TB HIV+	Number HIV-	MDR-TB HIV-	AOR	CI
Dubrovina. et al, 2008 (Ukraine)	Cross-sectional [a]	1540	Any	307	31.6%	1143	23.8 %	1.7	1.3-2.3
Valerieschoebel. et al, 1998 (france)	Case-control [a]	13344	Primary	893	1.2%	5864	0.3%	3.3	1.5-7.3
			secondary	107	11.2%	868	6.6%	1	0.5-2.0
Robert M.Granchi. et al, 2005 (calnifornia)	Cross-sectional [a]	28712	Any	2031	4%	27362	1.4%	0.98	0.78-1.23
Patrice Josephe. et al, 2006 (Haiti)	Cross-sectional [a]	330	primary	115	10%	166	3%	3.2	1.1-8.9
Andrew C.weltman. et al, 1994(newyork city)	Case-control [a]	172	any	78	26.9%	25	4%	2.71	1.09-6.79
Nino Mdivani. et al, 2008 (Georgia)	cross-sectional [a]	996	any	5	40%	227	28.6 %	1.4*	0.47-4.17
Catharina Hendrika. tal,2007 (netherland)	Cross-sectional [a]	7090	primary	308	1.6%	646	0.6%	2.78	1.09-7.1
Kliiman K. 2009 (Estonia)	Cross sectional [a]	1163	any	54	16.7%	914	18.8 %	1.57	0.80-3.11
S.J conaty. et al, 2004(England wales)	Case-control [b]	9541	Primary	274	3.6%	7936	1%	2.5	1.2-5.20
			secondary	19	21.4%	611	8.2%	2.8	0.6-11.9
k.weyer. et al, 2007 (s/Africa)	Cross-sectional [b]	5866	any	2700	3.4%	1939	2.9%	1.3	1.00-1.70
			Secondary	501	7.9%	418	5.7%	1.46	1.04-2.07

Ted Cohen. et al, 2010 (s/Africa)	Cross sectional [a]	240	Any	_	_	_	_	0.55	0.04-7.9
Beth Temple. et al (Uganda)	p.cohort [a]	410	Secondary	197	12.2%	212	13.2 %	0.9	0.5-1.6
Abdulhalik Werkicho (Ethiopia)	Case-control [a]	180	Any	71	63.4%	109	41%	3.1	1.02-9.4
RC brito. et al, 2010 (brazil)	Cross-sectional [a]	696	primary	187	8%	116	1.7%	4.6*	1.10-19.9
Enrico girardt. et al, 1996 (Italy)	Cross-sectional [a]	407	any	34	2.9%	87	5.9%	0.5	0.10-3.10
Souba dianda. et al, 2009 (burkinafaso)	Case-control [a]	360	any	66	9.1%	162	20%	1.43	0.22-9.45
Mac-Arthur.et al, 2001(mozambique)	Cross-sectional [a]	758	any	179	2.2%	530	3.2%	0.70	0.2-2.20
Jason R. Andrews. et al, 2010 (s/Africa)	Case control [a]	239	any	165	51.5%	74	66.2 %	1.40	0.5-4.0
Punnotok J. et al, 2000(thiland)	Cross sectional [a]	877	any	192	5.2%	685	0.44 %	11.9	4.3-33
M. casal.M. et al, 2005 (four europian country)	Case control [a]	414	any	45	42.2%	263	9.9%	1.96	0.9-4.2
yoshiyama T. et al, 2001(thiland)	Cross-sectional [a]	985	primary	377	8.4%	474	4.4%	2	1.1-3.5
			secondary	49	40.8%	85	32.9 %	1.4	0.68-2.92
Liuz Z. et al, 1998 (new jersey)	Cross sectional [a]	969	Any	556	4.9%	413	1.2 %	3.6	1.5-8.8
Jeffery Paul Taylor. et al, 1999 (texas)	Cross-sectional[a]	17425	secondary	2221	1.1%	15204	1.4%	0.78	0.5-1.2

N.B: ' a' represents institution based studies and 'b' represents population studies

* represents unknown HIV status patients or individuals considered as HIV negative

6.3. Summary Findings of Included Studies:

Latin America

In Haiti, a study found an increased risk for primary MDR-TB among the 115 patients with HIV co-infection (RR 3.2, 95%CI 1.1, 8.9), but no increased risk for acquired MDR-TB. Prevalence of acquired MDR-TB was actually higher among HIV-negative patients (35).

A cross sectional study in Brazil (Rio de Janeiro) showed strong association between HIV infection and primary MDR-TB, with 28.05% of 187 HIV co-infected and only 2.32% of 116 HIV negative tuberculosis patients (43). A study in Peru also found an association between HIV infection and MDR-TB, with 43.2% of 81 HIV co-infected and 3.9% of 965 HIV-negative patients having a diagnosis of MDR-TB (16). Important differences between groups included socio-economic status, TB treatment history, TB exposure, and use of medical services in the year preceding active TB. HIV co-infected patients were recruited from hospitals, whereas HIV negative controls were recruited from ambulatory clinics.

South Easter Asia

In Bangkok, Thailand, an increased rate (RR 11.9, 95% CI 4.3, 33) of MDR-TB was found among 192 HIV co-infected patients, compared to 685 HIV-negative patients and groups were comparable for TB risk factors (44). Another study in Northern Thailand found an association between HIV infection and primary MDR-TB (OR 2.0, 95% CI: 1.1, 3.5), but not acquired MDR-TB (OR 1.40, 95% CI: 0.68, 2.91) (45).There was no baseline comparison of risk factors among the 426 HIV-positive and 559 HIV-negative patients.

Sub-Saharan Africa

A case control study from Burkina Faso showed no difference in MDRTB prevalence rate among 66 HIV co-infected (9.1%) and 162 HIV-negative patients (20.4%) with AOR of 1.43 (CI, 0.22 – 9.45) after adjustment for age, treatment history, TB known contact, living outside Burkina Faso and occupation. they could not enroll enough number of TB patients and the collection of data was not performed uniformly for certain variables in all patients (alcohol abuse, traditional treatment, and previous TB contact) (21). Another study in Mozambique, of 179 HIV co-infected and 530 HIV negative TB patients, also found insignificant association

between MDR-TB and HIV infection with an odds ratio of 0.7 (95% CI: 0.2, 2.2). But baseline characteristics showed differences by HIV status in level of education, history of sexually transmitted diseases, and history of TB treatment (54).

Results from a national survey in South Africa found that there is no significant association of HIV infection and MDR-TB in all tuberculosis patients (aOR, 1.3; 95% CI 1, 1.7), but there is significant association between HIV infection and secondary MDR-TB in retreatment tuberculosis patients (aOR, 1.46; 95%,CI, 1.04 – 2.07) (46). A retrospective unmatched case control in South Africa demonstrated that HIV was an independent risk factor for XDR TB (aOR 8.2, CI 1.3–52.6), but not for MDR TB (aOR 1.4; CI 0.5, 4.0]) (53). The same finding was also recorded from prevalence and drug sensitivity of tuberculosis among patients dying in hospital in Kwa Zulu-natal in South Africa (aOR 0.55, CI 0.04–7.99) (55) and Kampala, Uganda (42). Another study in South Africa among gold miners, the MDR-TB rate was 5.3% among 207 HIV co-infected and 6.5% among 215 HIV-negative miners but only limited baseline characteristics and no statistical tests results were presented (17).

An unpublished MPH thesis in Ethiopia (Addis Ababa University) on hospitalized patients, which was unmatched case control study, observed strong association of HIV infection and multi-drug resistance tuberculosis (aOR of 3.1; 95% CI 1.02, 9.4). Potential confounders were adjusted (39).

Western Europe

Large and representative combined microbiological and surveillance datasets in two time periods (1993–1994 and 1998–2000) in England and Wales indicated that HIV infection was significantly associated with multidrug resistance in those with no previous tuberculosis (aOR of 2.5; 95% CI 1.2, 5.2) and being HIV positive was a modest predictor of multidrug resistance in those who have previous tuberculosis but was not statistically significant (aOR of 2.8; 95% CI 0.6, 11.9) (40).

A study on hospitalized TB patients in Rome, Italy, found that 2.9% of 34 HIV co-infected patients and 5.9% of 373 patients without documented HIV status had MDR-TB (OR 0.5, 95% CI: 0.1–3.2) (47). Patient characteristics were not compared by HIV status. The same finding was recorded from a prospective epidemiological case control study in four European Union

countries: France, Germany, Italy, and Spain between 1997 and 2000 (aOR 1.96; CI 0.9, 4.2) (28). A retrospective cross sectional survey from Netherlands documented that Multidrug resistance was significantly associated with HIV infection both before (odds ratio [cOR] 2.78, p = 0.033) and after adjustment by multivariate analysis for age, sex, and continent of origin (adjusted OR 3.43, p =0.015) (48).

A large survey (n= 13,344) conducted in the early 1990's in France, representing 80% of French public hospital beds, observed an association between primary MDR-TB and HIV (OR of 3.3; 95% CI: 1.5, 7.3), but not for acquired MDR-TB (OR 1.0; 95% CI 0.5, 2.0) when adjusted for sex, age, and region of origin (33). An eight years surveillance (1992-199) at national level in France with (n= 55571) also found that HIV co infection (odds ratio (OR) 2.02, 95% confidence interval 1.04–3.95) and female status (2.01, 1.12–3.62) were statistically associated with primary multi-drug resistance. Country of birth, age, sex, HIV co infection, site of TB and smear results were introduced in a backward logistic regression model to assess characteristics independently associated to primary or secondary multidrug resistance (34).

Eastern Europe

Across-sectional country-wide study in Estonia revealed an association of HIV infection with extensively drug-resistant tuberculosis (aOR 3.12; CI 1.31, 7.4) but not with multi-drug resistance tuberculosis (OR 1.57; CI 0.8, 3.11) (49). The prevalence of HIV was low in the sample. A cross-sectional prospective survey from Georgia documented that there is no significant difference in prevalence of MDR-TB by HIV status (OR 1.4; CI 0.47- 4.17) (32).

A study in Ukraine found significant association between HIV infection and MDR-TB (aOR 1.7; CI 1.3, 2.3), with 31.6% of 307 HIV co-infected and 23.8% of 1143 HIV-negative patients having a diagnosis of MDR-TB (10). Age, sex, place of residence, treatment history and civilian (civilian vs prisoners) status were entered to multivariate analysis.

United States

A case-control study based on chart review of patients with and without multidrug resistant tuberculosis, including outpatients and inpatients with culture-proved tuberculosis in New York, NY Hospital during 1991 and 1992 found statistically significant effects of HIV sero-positivity

as risk for multi-drug resistance tuberculosis in univariate analysis (odds ratio, 2.34; P=.0359) and after adjusting for demographic confounders (age, gender, race and previous treatment) (adjusted odds ratio, 2.71; 95% confidence interval, 1.09 to 6.79) (41). Similarly, in nearby New Jersey, HIV co-infected patients were at higher risk of MDR-TB (OR 3.6, 95% CI: 1.5, 8.8) (50). Factors such as previous TB, homelessness, and injection drug use were examined, but not stratified by HIV status.

Analysis of 38 291 TB cases reported from all 61 local health jurisdictions in California during 1994-2003 were found AIDS less frequently among MDR-TB cases in California compared with non–MDR-TB cases and the evidence was not substantial (aOR of 0.98; CI 0.98, 1.23) (51). Another retrospective cross-sectional study from Texas reported; tuberculosis patients with human immunodeficiency virus (HIV) infection were more likely to have rifampin resistance and less likely to have isoniazid resistance and multi-drug resistance than patients without HIV infection. No increased risk for multiple drug resistance was seen (aOR of 0.78; CI 0.5-1.21) (52). Residence, sex, age, race, history of homelessness and history of drug use were adjusted in the logistic regression model.

In summary 13 studies showed significant association between HIV/AIDS and MDR-TB but 16 studies showed no significant associations.

6.4. Assessing Heterogeneity and Publication Bias among the studies imputed into meta-analysis:

The studies showed good homogeneity using Cochrane Q test statistic (Q test p= 0.181) but low heterogeneity was observed up to 19.4% (I^2= 19.4%) which was indicative for using random-effects model. The distribution of the studies using traditional funnel plot (fig 2) and Begg's funnel plots (fig 3) showed symmetrical distribution of effect estimate and Beg rank correlation statistic (p = 0.33) showed no evidence of publication bias. But Egger weighted regression analysis (p=0.02) showed presence of publication bias.

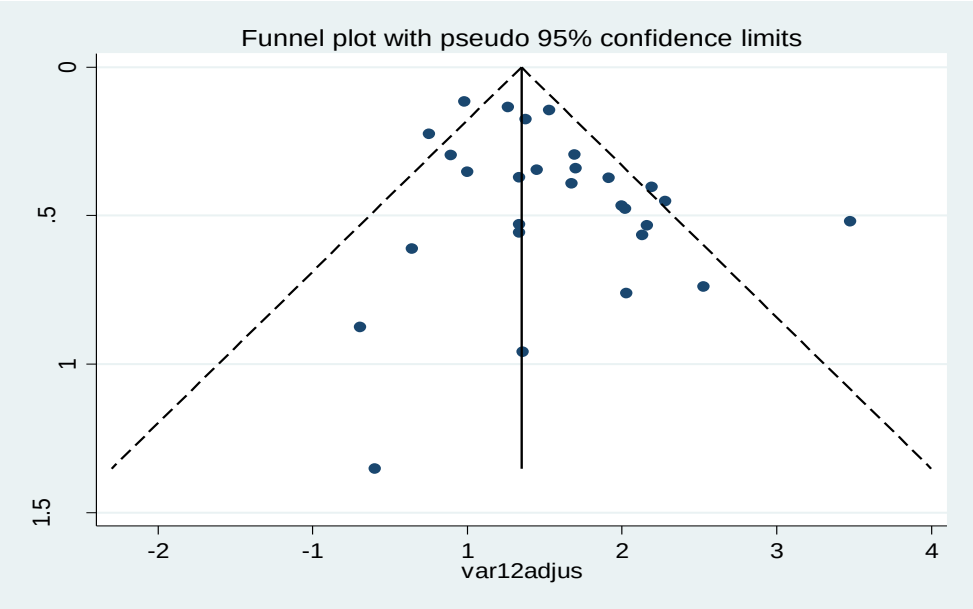

Figure 2: Funnel plot of with95% confidence limit; the horizontal line in the funnel plot indicates the effect estimate, while the sloping lines indicate the expected 95% confidence intervals.

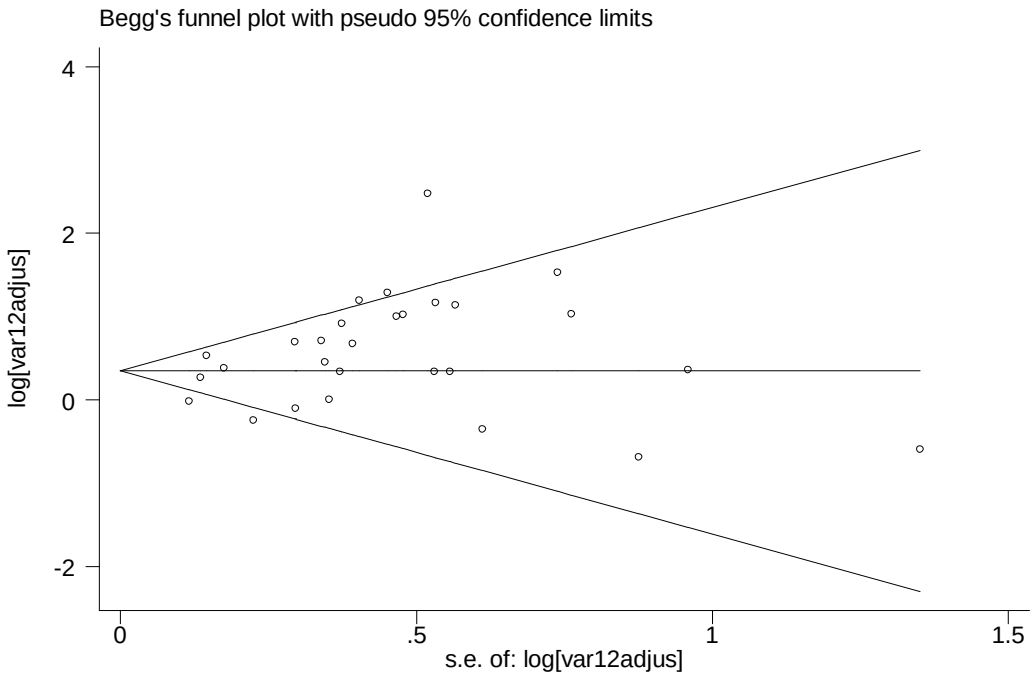

Figure 3: Begg's funnel plot with95% confidence limit;

The horizontal line in the funnel plot indicates the natural logarithms of the effect estimate, while the sloping lines indicate the expected 95% confidence intervals

According to Publication Bias in Meta-Analysis – Prevention, Assessment and Adjustments (56), if there is publication bias, the recommendation is displaying the data using cumulative forest plot (the studies sorted from the most precise to the least precise) and need to observe the effect of less precise studies (having large effect estimate) on the pooled effect estimate. So, in this meta-analysis if we limited the analysis to the larger studies, the relative risk would have been 1.21 (1.01, 1.40) and if we excluded the last two studies (Punnotok J. et al, 200 and RC.Brito. et al, 2010), the publication bias test (Egger weighted regression analysis) was 0.06 and the pooled effect estimate was 1.23 (1.04, 1.43). The clinical implications and even the statistical significance probably would have been the same with the pooled estimate, 1.24 including the last two studies mentioned above (figure 4). But there is still need to be interpreting the finding of this study carefully.

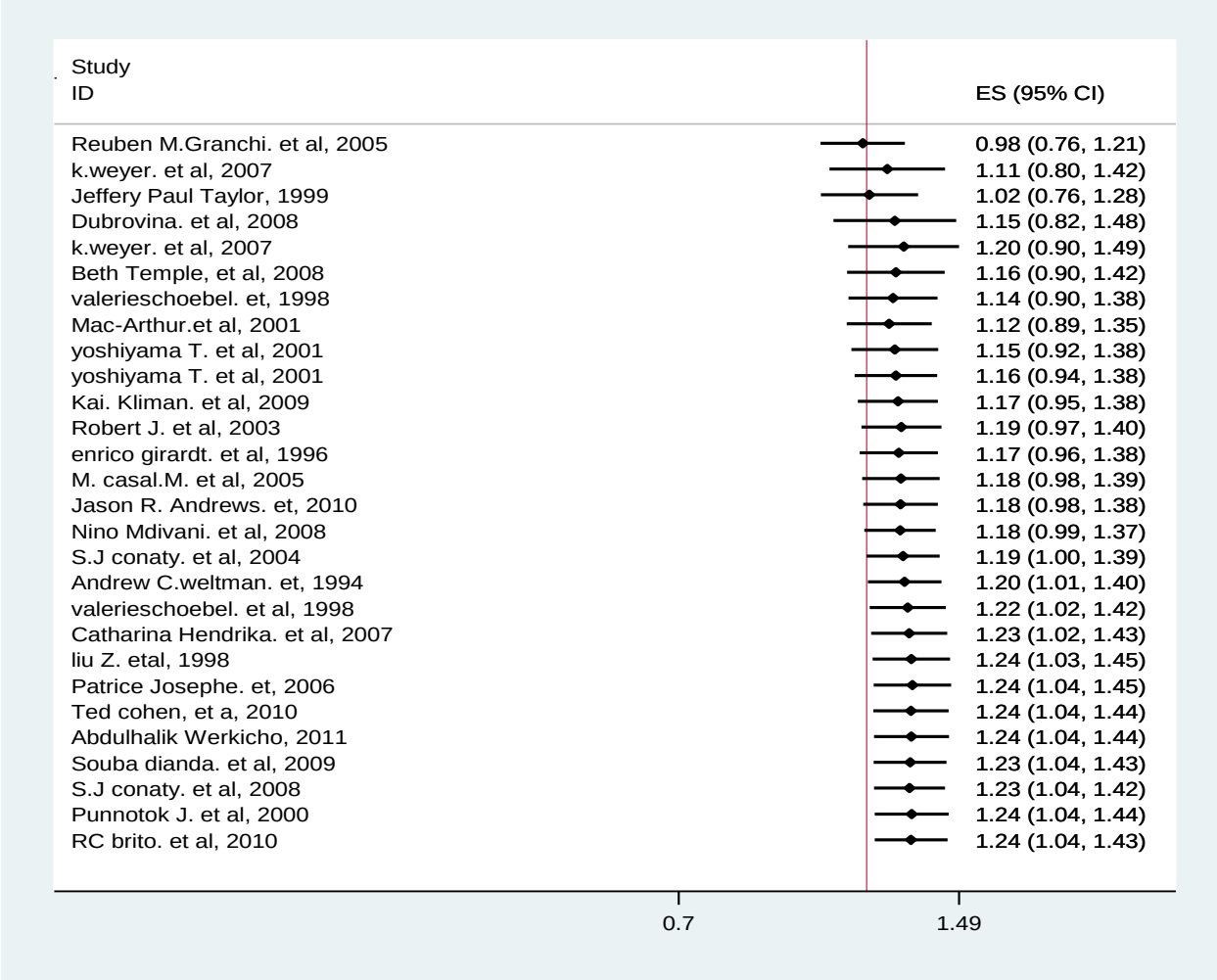

Figure 4: cumulative forest plot. The first row shows the effect based on one study, the second row shows the cumulative effect based on two studies, and so on.

6.5. The Association of HIV/AIDS and Multi-drug resistant Tuberculosis:

Based on the 24 observational studies included in this meta-analysis, the pooled odd ratio according to random effect DL model was 1.24 (95% CI 1.04 to 1.43) (Figure 5). In this plot, the studies have been listed from most precise to least precise, so that larger studies appear toward the top and smaller studies appear toward the bottom. This has no impact on the analysis, but allows us to get an initial sense of the relationship between sample size and effect size.

Based on sub group analysis; we found moderate heterogeneity of effect estimate from studies within each study design (between study variance accounted for 33% of the total variance among cross sectional studies and surveillance) and low heterogeneity of effect estimate (I^2=19.6%) of the total variance among institution based studies. The pooled effect estimate for primary MDR-TB and HIV (7 studies) was 2.28 (95% CI 1.52, 3.04). The pooled effect estimate for population based studies (2 studies) was 1.38 (95% CI 1.09, 1.66). The sub group analysis output based on study characteristics and quality assessment criteria were summarized in table 2.

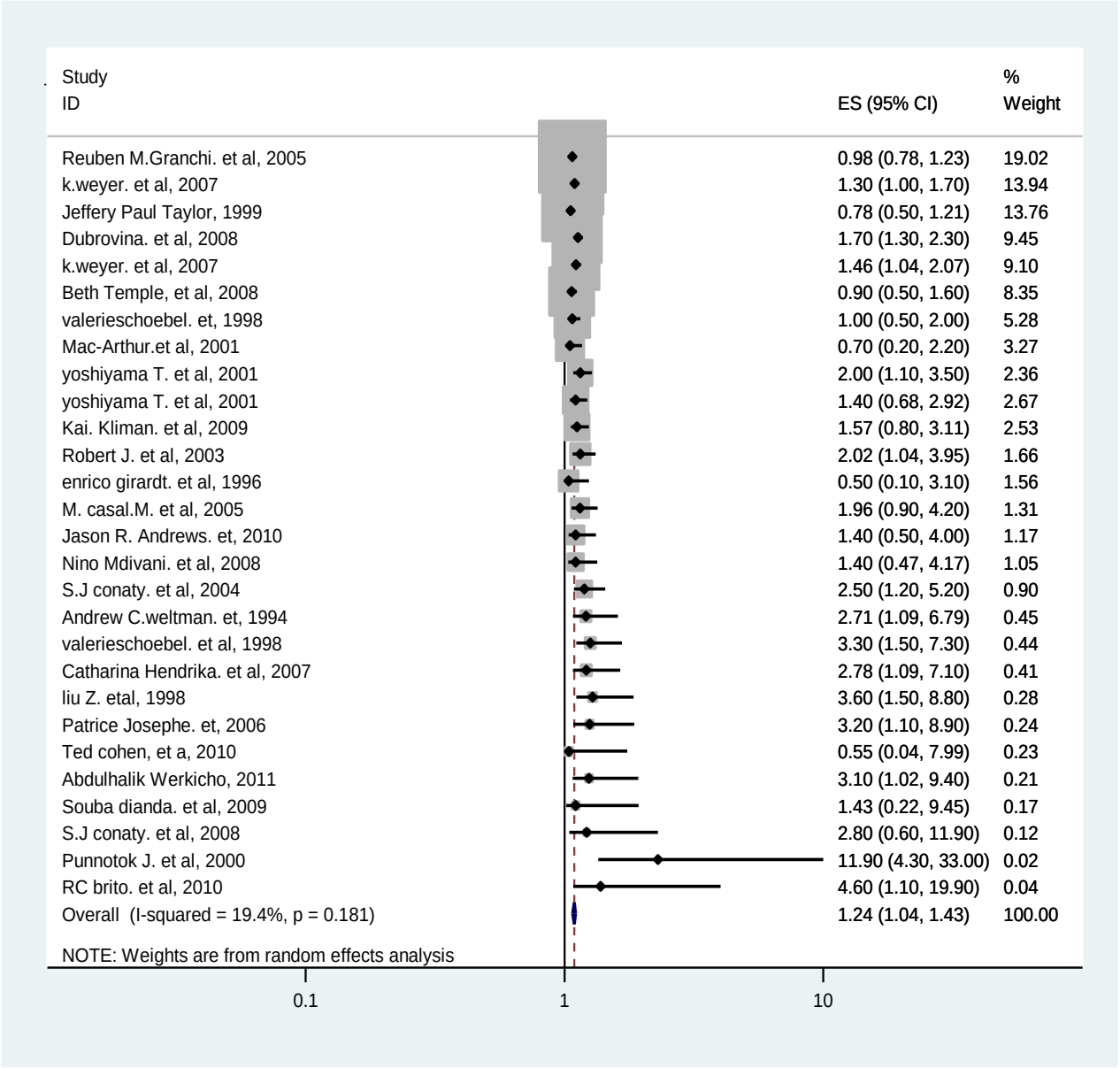

Figure 5: Forest Plot of the 24 observational Studies That Quantitatively Assessed the Association between HIV/AIDS and multi-drug resistance tuberculosis.

Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. Arrows indicate that the bars are truncated to fit the plot. The diamond is centered on the summary OR of the observational studies, and the width indicates the corresponding 95% CI.

Figure 6 summarizes sub-group analysis of the adjusted effect estimate of the 24 observational studies by study base. We found no heterogeneity of effect estimate from population based studies (between study variance 0% and Cochrane Q test statistic (P=0.628)). There is no significant heterogeneity of effect estimate from institution based studies (between study

variance accounted for 19.6% and Cochrane Q test statistic (P=0.194)). The forest plot showed that HIV/AIDS is positively associated with multi-drug resistance tuberculosis among population based studies with summary OR= 1.38 (95% CI, 1.09 – 1.66).

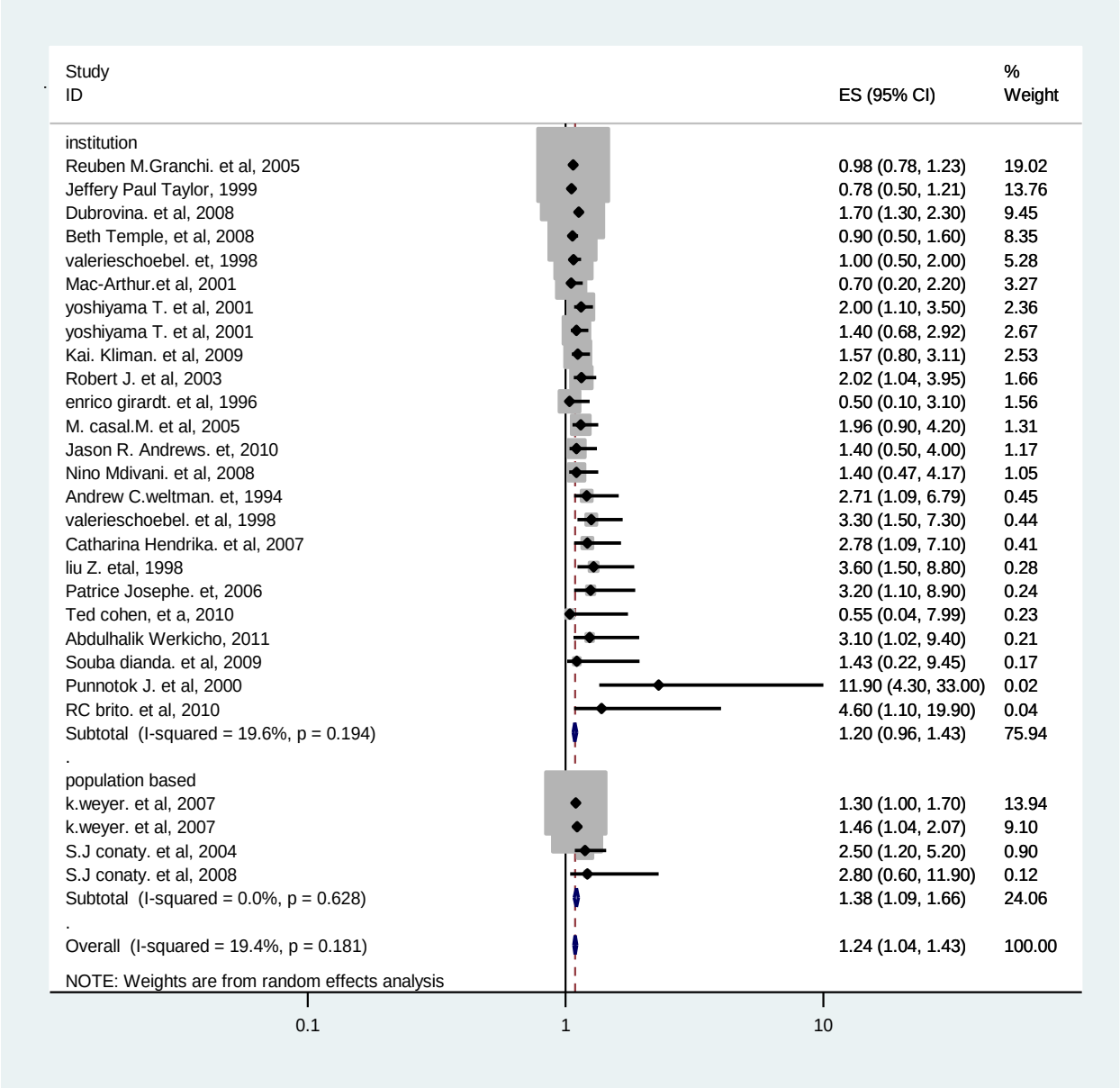

Figure 6: Forest Plot of the 24 Studies That Quantitatively Assessed the Association between HIV/AIDS and multi-drug resistance by Study base.

Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. Arrows indicate that the bars are truncated to fit the plot. The diamond is centered on the summary RR of the studies for each study design, and the width indicates the corresponding 95% CI.

Figure 7 summarizes measure of association on HIV/AIDS and MDR-TB by multi-drug resistance type based on the data presented from 24 studies. The plot demonstrated that there is significant positive association between HIV/AIDS and primary MDR-TB with summery OR of 2.28 (95% CI, 1.52 – 3.04) and there is positive association between HIV/AIDS and secondary (acquired) MDR-TB but not significant (summery OR=1.02, 95% CI; 0.80, 1.24). There is no heterogeneity at all (Q test, p=0.791 and I^2=0 %) for any type MDR-TB and (Q test, p=0.965 and I^2=0.0 %) for primary MDR-TB.

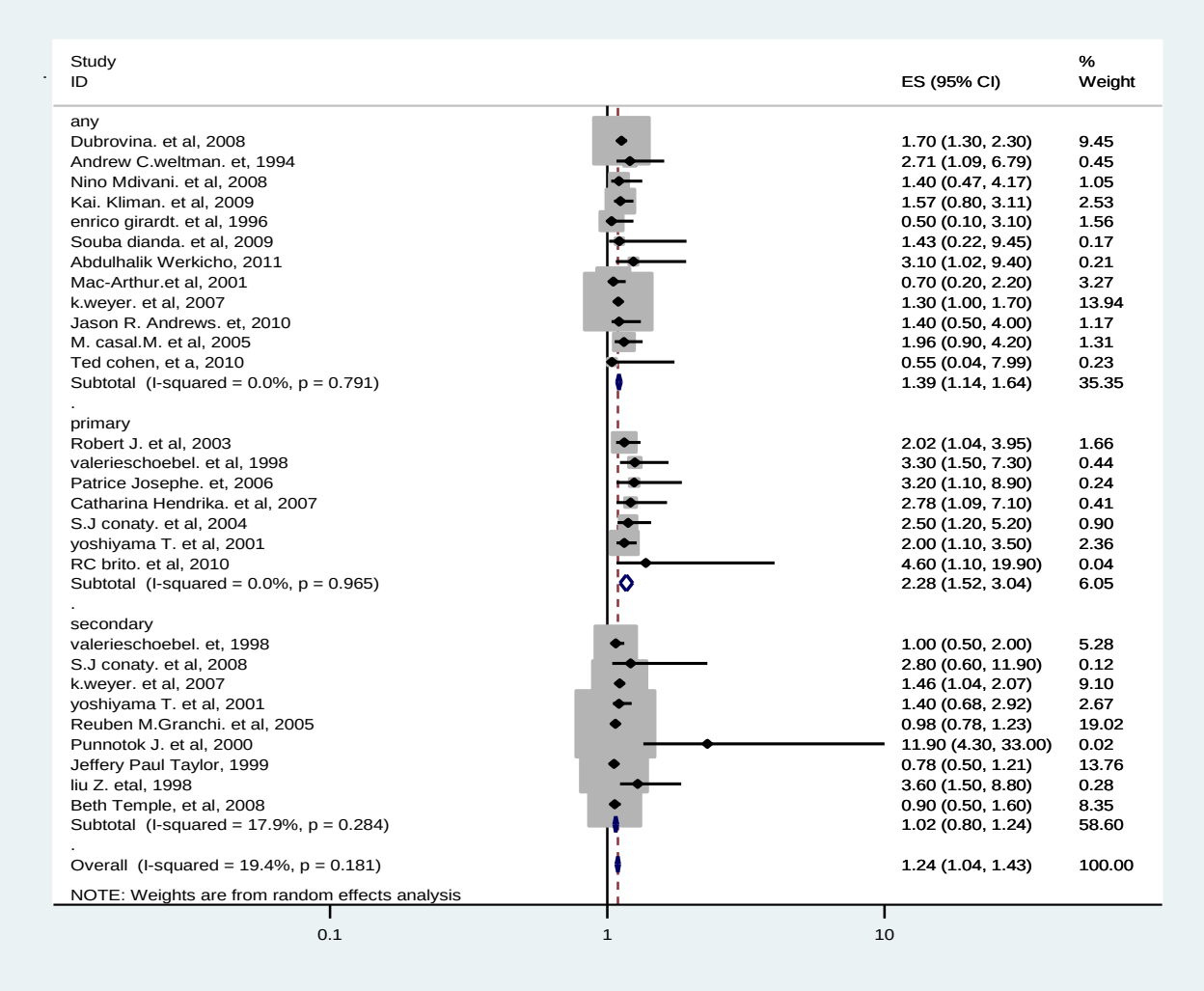

Figure 7: Forest Plot of the 24 Studies That Quantitatively Assessed the Association between HIV/AIDS and multi-drug resistance tuberculosis by MDR-TB type.

Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. Arrows indicate that the bars are truncated to fit the plot. The diamond is centered on the summary RR of the studies for each study design, and the width indicates the corresponding 95% CI.

Figure 8 summarize measure of association on HIV/AIDS and MDR-TB by study design based on the data presented from 24 studies. The plot demonstrated that there is positive and significant association between HIV infections and MDR-TB among cross-sectional and surveillance studies (summery OR 1.36; CI 1.02, 1.49) but not among case-control studies (summery OR 1.5; CI 0.93, 2.06).

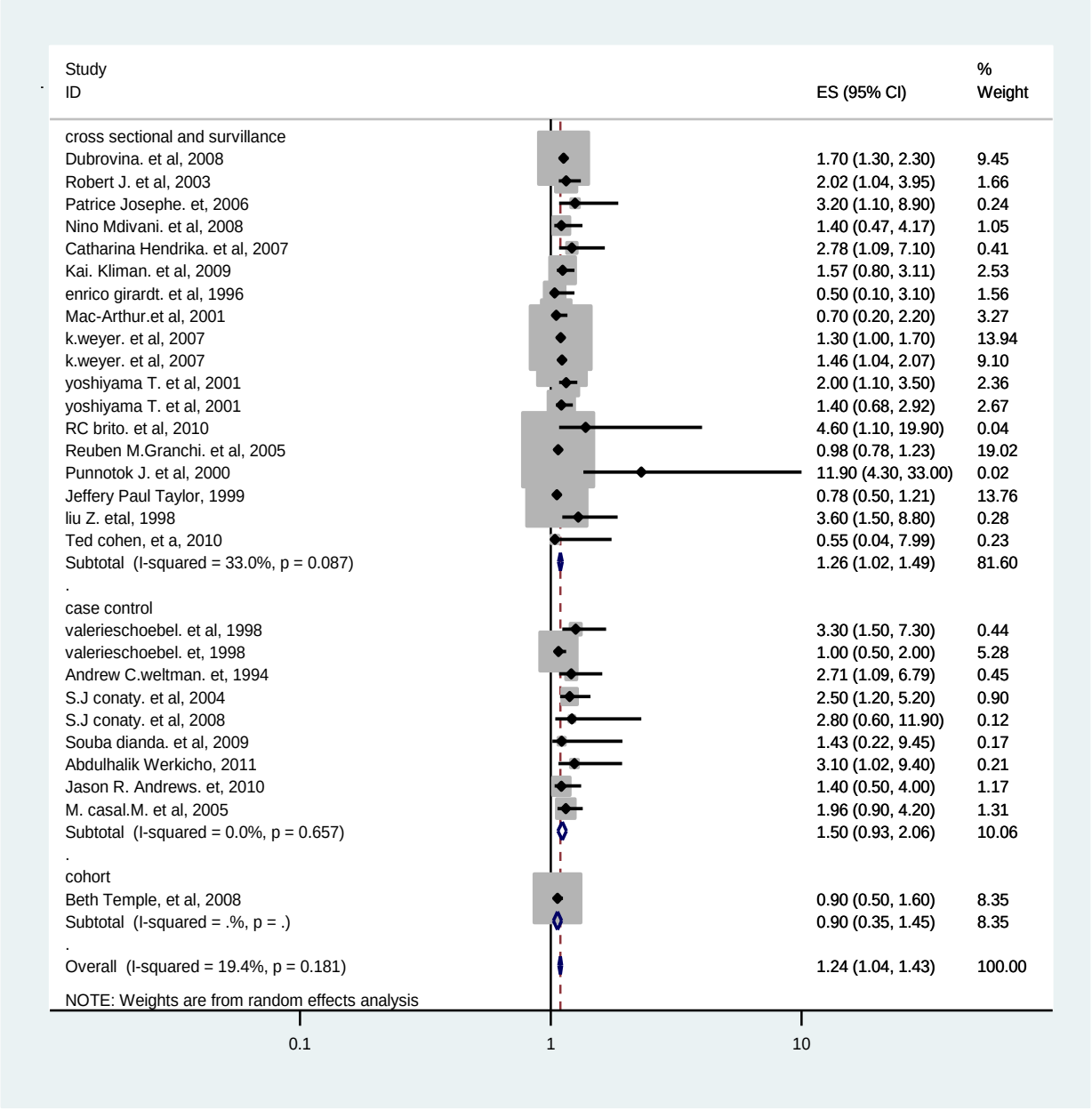

Figure 8: Forest Plot of the 24 Studies That Quantitatively Assessed the Association between HIV/AIDS and Multi-drug resistance tuberculosis by Study Designs.

Table 2: Quality assessment and sub group analysis; HIV/AIDS and multi-drug resistance tuberculosis.

Measure or Outcome	Study Characteristics (Number of Studies)	Summary OR	95% CI	I^2
Outcome	Primary MDR-TB (7)	2.28	1.52 – 3.04	0 %
	Secondary MDR-TB (9	1.02	0.80 - 1.24	17.9 %
	Any (12)	1.18	1.14 - 1.64	0 %
Type of study	Case-control (9) and cohort studies (1)	1.20	0.79 – 1.58	0%
	Cross sectional and Surveillance (18)	1.26	1.02 – 1.49	33%
Study base	Population (4)	1.38	1.09 – 1.66	0 %
	Institution (24)	1.20	0.96 – 1.43	19.6%
Adjustment for	Demographic and tuberculosis related variables (10)	1.51	1.02 – 1.99	0 %
	Demographic and socio-economic variables (8)	1.33	0.7 – 1.96	0 %
	Demographic, Tuberculosis related and socio-economic variables (8)	1.23	0.96 – 1.56	54.3%
Selection of control	From hospital and discharge records (7 study)	1.39	0.80 – 1.99	0 %
	From population (2 study)	2.53	0.65 – 4.42	0%

I2 - Percentage of total variance due to between-study heterogeneity

OR - odds ratio of the summery estimate

7. DISCUSSION

This review and Meta-Analysis addressed articles on the association of HIV infection and multi-drug resistance tuberculosis using 24 selected studies. Twenty four studies were identified from sixteen countries and summarized the evidence on the association between HIV infection and MDR-TB. According to the results of this meta-analysis, the odds of having MDR-TB among HIV positive cases was higher by 24% and this was statistically significant as pooled OR of 1.24 (95%, 1.04 – 1.43) regardless of study designs, study base, and multi-drug resistance tuberculosis type. But about 81.4% of the weight of the pooled odds ratio of this meta-analysis was comes from cross sectional and surveillance studies which have low power to assess predictors. The subgroup analysis further showed that HIV infection was a risk factor for multi-drug resistance tuberculosis among population based studies than among institution based studies. The pooled risk of primary multi-drug resistance tuberculosis was two times higher in HIV infected population than those not infected with high homogeneity (I^2= 0%) between studies.

There was publication bias despite of several studies observed no relationship between MDR-TB and HIV infection included in this review. The cumulative meta-analysis also showed that the increased risk in the larger studies was 21 % and 23% for all studies but Punnotok J. et al, 200 and RC.Brito. et al, 2010. There was evidence of bias in pooled estimate based on all studies, and the risk was probably somewhat higher than reported in highly precise studies, but there was no reason to doubt the validity of the core finding, that HIV/AIDS was associated with a clinically and statistically important increase in the risk of multi-drug resistance tuberculosis.

This meta-analysis, unlike previous reviews (57), includes ten recent studies that had examined the association of HIV infection and MDR-TB and generated over all pooled summary estimate regarding the overall association between HIV infection and multi-drug resistance tuberculosis. Additionally a rigorous sensitivity analyses was done to identify important sources of heterogeneity.

The previous meta-analysis mentioned above (57) did not report an overall association between MDR-TB and HIV due to high heterogeneity across studies. But their subgroup analysis results suggest that HIV infection was associated with primary MDR-TB 2.72 (95% CI 2.03, 3.66, p

value for heterogeneity = 0.356) and not statistically associated with acquired MDR-TB and HIV 1.17 (95% CI 0.86, 1.6, p-value for heterogeneity = 0.188). The sub group analysis result (for primary and secondary MDR-TB) of the present meta-analysis is consistent with the above systemic review in that HIV infection is significantly associated with primary multi-drug resistance tuberculosis (pooled OR 2.28, 95% CI 1.52 – 3.04; I^2 = 0%) and positively associated but not significant with secondary MDR-TB (pooled OR 1.02, 95% CI 0.80 – 1.24; I^2 = 17.9%). This could be explained by the fact that HIV infected cases progress rapidly to disease and in settings where MDR-TB is prevalent, either in the general population or in the local population such as a hospital or a prison. This may lead to rapid development of a pool of drug resistant TB patients, or an outbreak. Furthermore, people living with HIV may also be more likely to be exposed to MDR-TB patients, due to either to increased hospitalizations in settings with poor infection control or association with peers who may have MDR-TB, including in penitentiary settings (5).

Several biological mechanisms also linking drug resistant TB to HIV infection have been suggested. People with HIV infection progress from tuberculosis infection to active disease faster than immune competent people, the prevalence of drug resistance in HIV-positive patients largely depends on recently circulating strains, and so will be greater than in HIV-negative patients. Drug mal-absorption in HIV infected patients, especially rifampin and ethambutol, can lead to drug resistance and has been shown to lead to treatment failure (29).

Another meta-analysis(23) on risk factors for multi-drug resistance tuberculosis in Europe documented that MDR-TB patients were more likely to be HIV positive with pooled risk estimate of (from 6 studies) 3.52 (95% CI 2.48 – 5.01 and Q test, p= 0.089; I^2 =45.4%). The finding in present meta-analysis goes in line or comparative with this study but the magnitude of the pooled estimate was less than the above mentioned study. This could be because the present meta-analysis has included 16 additional and recent studies which contribute to its more precise estimate while the inclusion of studies having significant association in the former meta-analysis (23) might have led to selection bias.

Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007–2010 (surveillance data from 17 countries and 1 territory were combined)(58) reported that the odds of having MDR-TB among HIV-positive cases were found to be 40% higher than among HIV-

negative cases (pooled odds ratio, OR: 1.4; 95% CI: 0.7–3.0; OR consistent across countries, I^2 = 23.2%; *P*-value = 0.19), but the difference was not significant. The possible explanation for the discrepancy of the findings between this study and our meta-analysis could be methodological difference of the studies included in the meta-analysis and the study was based on patients' visiting health institutions. Around 18.4% of the weight the summery odd ratio of our meta-analysis comes from case-control studies and cohort studies.

The finding of the data analysis should be interpreted in the context of both inherent limitation of the original studies and the current review and meta-analysis.

8. LIMITATIONS AND STRENGTHS

8.1. Strengths:

The main strengths of this meta-analysis were;

- There was good homogeneity between studies
- Rigorous subgroup analysis was made
- The studies included in this systemic review and meta-analysis were from different region of the world include gray literature
- Some of the studies were reported data stratified by HIV/AIDS status.
- Data and information's were abstracted uniformly using a predetermined and pretested standard format.

8.2. Limitations:

There are several potential limitations to this study. The analysis was based on estimates derived from observational studies that are vulnerable to confounding by variables associated with both HIV infection and MDR-TB. To address the issue of potential confounding, a sensitivity analysis was performed in which separate summary estimates was reported for the studies that adjusted for important potential confounders and those that did not. Studies that controlled for socioeconomic status in a multivariable model found that the adjusted effect of HIV infection was reduced. Although it is not possible to exclude the possibility of residual confounding by unmeasured confounders in these observational studies, such as other chronic diseases that often coexist with HIV, the effect of HIV infection on MDR-TB risk was found to persist even after adjustment for multiple potential confounders that are likely to be correlated with unmeasured factors.

Seven of the studies included in this meta-analysis were case-control studies. These used different approaches to the selection of controls, including sampling from hospitals, discharge records, department of health records and the general population. Sampling controls from hospital or discharge records may have introduced a Berkson bias—selection biases that can occur when both the exposure and the outcome are associated with attendance at a health-care facility from which cases and controls are recruited. Since HIV infection can lead to multiple

health problems, the prevalence of HIV infection is likely to be higher among persons attending clinics or being admitted to hospitals than it is in the general population. This bias would be expected to result in an underestimation of the effect of HIV infection on MDR-TB. When we compared the effect estimates for studies stratified on the basis of the control selection strategy, we found that studies that had not used population-based controls tended to report lower effect estimates even though number of population based case control in this meta-analysis were two, consistent with our expectation of a bias toward the null among studies that used hospital and discharge records.

Other potential sources of bias include possibly misclassification of both exposure and outcome status. As the primary aim of some studies was not to assess the association between HIV infection and MDR-TB, studies could have suffered from misclassification bias due to inclusion of patients with unknown HIV status, and participation bias when HIV infected individuals were more likely to be tested for drug resistance.

9. CONCLUSION AND RECOMMENDATIONS

In summary, this study found consistent but marginal evidence for an increase risk of multi-drug resistance tuberculosis among people with HIV infection despite some heterogeneity was observed among cross sectional and surveillance studies and institution based studies. Sub-group analysis also showed that HIV infection was positively and significantly associated with multidrug resistance tuberculosis among population based studies and also with primary multi-drug resistance.

The results have programmatic implications and public health importance;

There should be strong collaboration between HIV/AIDS and TB control programs and capacity for concomitant MDR-TB and antiretroviral treatment needs to be scaled up and strengthened.

Ensure early case detection, diagnosis through quality-assured bacteriology and provide standardized treatment with supervision and patient support.

Good infection control program need to be implemented and there also need to have close follow up to reduce risk of spread of MDR-TB, especially in HIV positive patients, particularly in clinics and hospital.

Since the effect of HIV/AIDS on MDR-TB was marginal, the association of HIV infection and MDR-TB need to be further studied by including prospective and large scale population based studies by stratifying the data by HIV status to assess the relationship between HIV infection and MDR-TB at population level.

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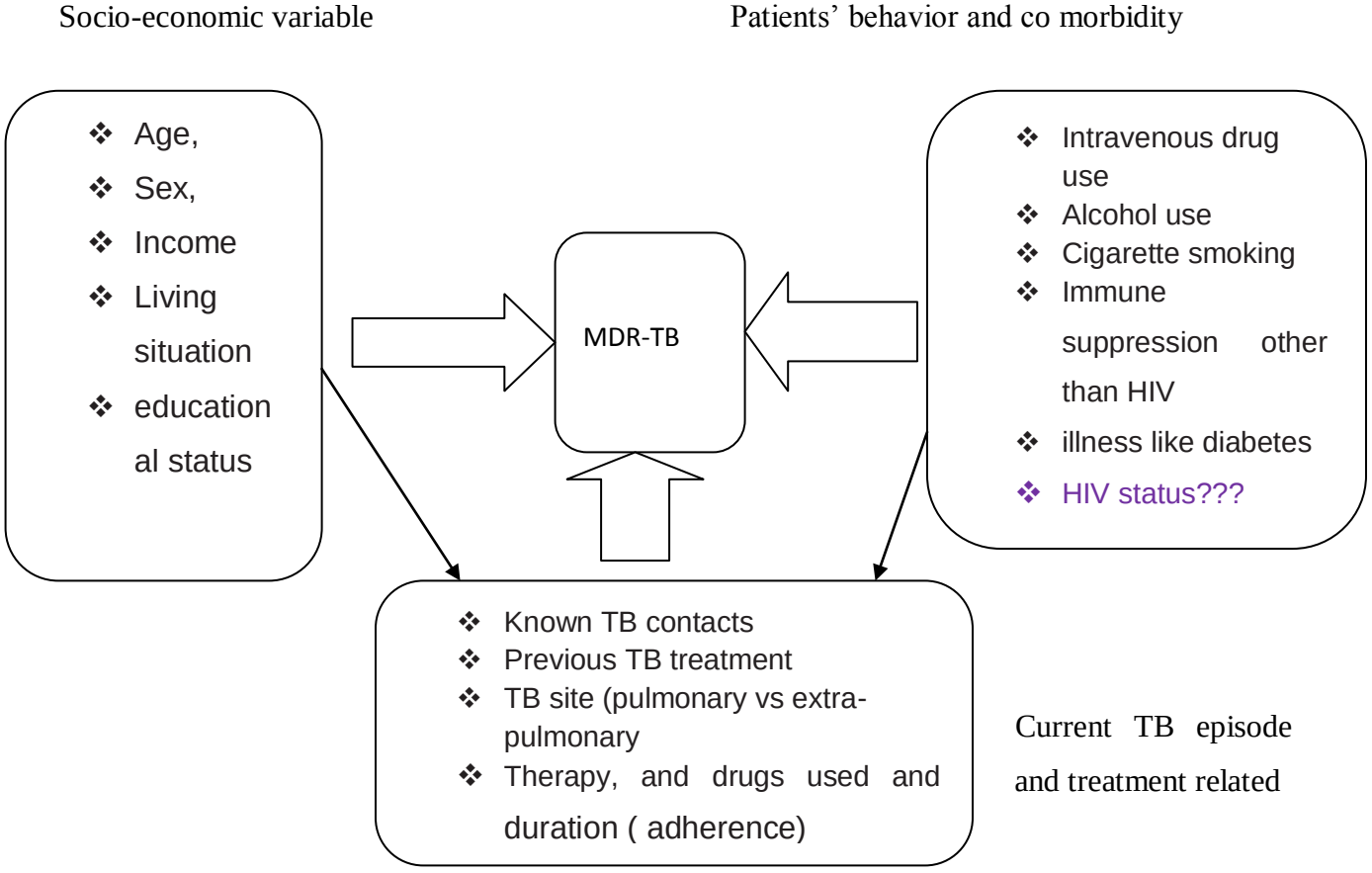
ANNEXES

ANNEX 1. Conceptual framework on risk factors of multi-drug resistance tuberculosis



ANNEXES 2: Data Extraction Sheet

Name of Reviewer:	
Title of Paper:	
Author(s):	

Date of Publication:	
Source of Publication:	
Country (developing vs developed)	
study design	
Study period	
study base (population-based or hospital-based)	
Methods of confirmation of MDR-TB status	
Methods of confirmation of HIV status	
Sample size and Characteristics:	
Sampling of study unit (controls vs case and non-exposed vs exposed)	
Selection of controls for case control study	
number of exposed/unexposed people or cases/controls	
data collection procedure	
TB form (pulmonary, extra pulmonary);	
Type of drug resistance TB	
Type of MDR-TB (primary or acquired)	
Total number of HIV positive patients	
Total number of HIV negative patients	
response rates	
Proportion of MDR-TB among HIV positive patients	
Proportion of MDR-TB among HIV negative patients	
measure of association like OR/ RR, X2 with its confidence interval (CI)	
P-values	
Adjusted variables	
proportion of exposed and who developed the disease for different categories and standard deviation (SD) standard error (SE	

DECLARATION

I, undersigned, declared that this thesis is my original work in partial fulfillment of the requirement for the degree of master of public health. All the sources of the material used for this thesis and all people and institutions who gave support for this work are fully acknowledge

Name: **Asmamaw Moges (BSc)**

Signature: _____

Place of submission: _____

Date of submission: _____

Approval of the primary advisor

This thesis work has been submitted for examination with my approval as university Advisor.

Advisor's name: **Damen Hailemariam (Professor)**

Signature: _____

Date: _____