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Jolie Siegel Date

Influence of HIV Co-infection on Tuberculosis Treatment Outcomes in Children: A Systematic Review and Meta-analysis of the Literature

By

Jolie Siegel
Degree to be awarded: MPH

Global Health

_____

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Influence of HIV Co-infection on Tuberculosis Treatment Outcomes in Children: A Systematic Review and Meta-analysis of the Literature

By

Jolie Siegel

B.A., State University of New York at Geneseo, 2015

Thesis Committee Chair: Kenneth G. Castro, MD, FIDSA

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Abstract

Influence of HIV Co-infection on Tuberculosis Treatment Outcomes in Children: A Systematic Review and Meta-analysis of the Literature

By Jolie Siegel

Introduction: Tuberculosis (TB) is an infectious disease that kills thousands of adults and children every year. Although treatment is available, effectiveness can be complicated by a range of factors such as co-infection with human immunodeficiency virus (HIV). When compared with adult TB patients who are not infected with HIV, co-infection with HIV has been shown to be associated with worse treatment outcomes. However, the influence of HIV on treatment outcomes in children has not yet been clearly established. This meta-analysis and systematic review was conducted in order to answer this question.

Methods*:* Search terms were developed and used in the databases PubMed, Embase and Cabi. Articles were retrieved and reviewed using predetermined inclusion and exclusion criteria. Both EndNote X7 and Covidence were used to sort articles for selection. Pertinent information was abstracted from the final included studies and reported in a Summary of Findings Table.

Results: The literature search initially identified 896 articles. After review, 25 articles met the inclusion criteria and were selected for this review. A qualitative description of the articles was written and a meta-analysis performed. The summary risk ratio of all included studies for comparison of favorable treatment outcome rates was 0.775 (95% CI: 0.70- 0.86). When compared with children who had TB but no HIV infection, those with HIV infection were more likely to experience unfavorable treatment outcomes, with the resulting summary risk ratio found to be 1.77 (95% CI: 1.40- 2.24). Similarly, when comparing children who had TB but no HIV infection, those with HIV infection had significantly higher mortality; the summary risk ratio for comparison of death rates was 3.26 (95% CI: 2.57- 4.14).

Conclusions*:* Children with TB disease and HIV co-infection are more likely to experience unfavorable treatment outcomes or die of TB than children without HIV co-infection. Additionally, children with TB disease and HIV co-infection were also less likely to experience favorable treatment outcomes. Future research should examine the influence of ART on treatment outcomes and whether this additional treatment for underlying HIV changes the observed findings.

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Jolie Siegel

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Introduction

Background Information

Tuberculosis (TB) disease is a very important public health problem that continues to plague the global community. This disease is caused by *Mycobacterium tuberculosis* complex, a bacterial pathogen which is primarily transmitted from person-to-person via the airborne route.[1] Upon infection, most people with an intact immune system are able to contain the infection and remain latently infected (this condition is also known as latent TB infection). However, an estimated 5-10% of those infected experience lifetime risk of progression to TB disease. Clinically evident TB disease most commonly affects the lungs and respiratory system, but can also occur in any organ system of the human body. Several conditions have been shown to accelerate the risk of TB disease progression, including infection with human immunodeficiency virus (HIV), diabetes mellitus, malnutrition, chronic obstructive lung disease, and other causes of immunodeficiency. It has been estimated that approximately one quarter of the global population harbors latent TB infection.[2] Additionally, an estimated 10 million people were reported to the World Health Organization (WHO) with incident TB disease in 2017, along with 1.6 million attributable deaths.[3]

Perhaps equally distressing are the statistics reflecting the number of children afflicted and killed by TB disease. According to the most recent data, in 2017 WHO reported that an estimated 1 million children became ill with TB and 230,000 died from infection during that year.[3] Due to advances in medicines and healthcare, infections, disease, and deaths due to TB are both preventable and curable. Today, there is a range of treatment regimens available to cure people with TB disease. The most commonly prescribed treatment regimen, for TB forms that

are not resistant to drugs, includes a combination of the drugs isoniazid, rifampin, ethambutol and pyrazinamide taken for about 6 to 9 months.[1]

Despite the availability of TB treatment, successful outcomes can be complicated due to a range of factors, one of which is co-infection with HIV.[4] HIV is a retrovirus that weakens the human immune system, leaving the infected person vulnerable to contracting and dying from opportunistic diseases, such as TB. Indeed, TB is the leading cause of death for people living with HIV, killing approximately 300,000 people in 2017.[3]

The association between tuberculosis disease in the context of HIV co-infection and suboptimal TB treatment outcomes has long since been documented. In 1987, a position paper of the American Thoracic Society summarized past evidence regarding the interaction between HIV and TB and concluded that HIV is associated with an increased risk of TB morbidity.[5]

Since then, additional studies have corroborated this evidence. In 2012, Sanchez and colleagues examined TB treatment outcomes in 161,481 Brazilian adult patients diagnosed with TB not co-infected with HIV, and compared outcomes with those who had HIV co-infection.[6] Results of this retrospective study showed that patients with HIV were 3.09 times more likely to have unfavorable TB treatment outcomes (death, treatment default or transfer) as compared to patients without HIV. Another more recent meta-analysis examined TB treatment outcomes in adults and children infected with HIV and multidrug resistant TB (MDR-TB) compared with MDR-TB patients without HIV.[7] The review examined 30 studies and concluded that although treatment success rates were similar among the HIV co-infected and those without HIV infection, mortality was significantly higher in the HIV co-infected group.

Although the negative TB treatment outcome correlation with HIV co-infection has been well documented in adults, as evidenced in the afore mentioned studies, whether this association

exists in children remains an under-researched area where the existing evidence provides uncertain results. In a 2001 study examining pulmonary disease in HIV-infected African children, Graham and colleagues concluded that based on the lack of evidence, the association between pulmonary TB disease treatment outcomes and HIV infection is unclear and that more research is necessary before certain conclusions can be drawn.[8]

Another study published in 2005, by Hesseling and colleagues provided more decisive, though still limited, evidence on the topic. [9] In the study, the records of 87 children with both TB disease and HIV infection were examined. The researchers determined that based on the number of deaths and poor outcomes, HIV co-infected children were at high risk of death during and after treatment for TB disease. Despite these findings, it must be acknowledged that no comparison group of children without HIV co-infection was present, limiting the interpretation of the conclusions.

Another study by Mukadi and colleagues examined infection development, clinical presentation and outcomes of TB disease treatment in children from Côte d'Ivoire.[10] This study included a comparison group of HIV negative children. It was found that children co-infected with HIV and TB disease were more likely to die than those with TB disease in the absence of HIV infection. Raw data for this finding were not provided and hence, the study was not included in the following meta-analysis and systematic review.

Another article by Venturini and colleagues published in 2014 summarized the limited research on the topic of how HIV influenced TB treatment outcomes in children.[11] Venturini reported on how past studies found that HIV co-infection did in fact cause more severe disease and higher risk of mortality in HIV positive children with TB disease as compared to children with TB disease and not infected with HIV. However, the authors concluded that these findings

were based on relatively limited evidence, especially when comparing TB treatment outcomes in HIV co-infected children with multi-drug resistant strains of TB disease.

Based on the limited scope of literature summarized above, it is evident that additional and more definitive comparative studies are needed on the topic of how HIV influences TB disease treatment outcomes in children. This topic is an especially important area because of the need to inform optimal treatment outcomes in children by relying on evidence-based guidelines.[12] Treatment for adults and children with drug-susceptible TB is similar in types of drugs, however, dosages of these medications are based on the weight of the patient.[13] Similarly, while symptoms are often comparable between adults and children, very young children are at risk of more severe disease as a result of less developed immune systems. These worse outcomes due to TB disease include development of meningitis or disseminated disease, and more rapid disease onset when compared to adults.

Objectives

In this review, favorable TB disease treatment outcomes, unfavorable TB disease treatment outcomes and mortality in HIV co-infected children will be compared to outcomes in children without HIV infection. This review aims to ascertain if TB disease treatment outcomes are significantly influenced by HIV co-infection status in children. To this end, the proposed systematic review will answer the following questions:

1. Are children with TB disease and HIV co-infection less likely to experience favorable TB treatment outcomes as compared to children with TB in the absence of HIV infection?

2. Are children with TB disease and HIV co-infection more likely to have unfavorable treatment outcomes than children with TB in the absence of HIV infection?
3. Are children with TB disease and HIV co-infection more likely to die than children with TB in the absence of HIV co-infection?

Results have the potential to provide evidence-based guidance to inform public health policy revisions that would optimize TB disease treatment outcomes in HIV co-infected children.

Methods

Literature Search

A literature search was conducted using PubMed, Embase, and CABI electronic databases. The research questions were formulated using the PI(E)CO Framework (Population, Intervention (Exposure), Comparison and Outcome).[14]

In this study the population of interest (P) included children who had TB disease. The WHO TB data characterizes children as individuals equal to or less than 14 years of age.[3] However, for this review, the cut-off of 17 years of age was used because several of the studies included characterized children as either less than or equal to 15 years of age, and one study, as patients less than 17 years of age.

Due to the differing national guidelines for diagnosing TB, there was no consistency on how TB status was defined. In general, studies included diagnosis by way of a combination of factors including detection of acid-fast bacilli (AFB) or *Mycobacterium tuberculosis* from sputum or gastric aspirates, tuberculin skin testing and suspected clinical signs and symptoms

consistent with TB. The exposure (E) of interest was HIV positive status in addition to TB disease diagnosis.

The comparison category (C) included persons who had TB disease but were HIV-negative. The outcomes of interest (O) included TB cure and completion of therapy (combined in a single category as 'favorable treatment outcome'), unfavorable treatment outcome, and mortality.

The most common definitions of TB cure were smear- or culture-negative status in the last month of treatment and on at least one previous occasion. Most studies defined treatment completion as evidence of finished therapy without evidence of failure and with no record of a positive smear or culture result in the last month of treatment.

The "unfavorable treatment outcome" was defined as death, loss to follow up, or incomplete or failed treatment. Although some studies distinguished TB-specific deaths from deaths due to other causes, a number of studies did not report cause-of-death information; for this reason outcome of interest in this review is all-cause mortality.

Studies were included in the review and meta-analysis if they 1) were based on a population under 18 years of age, 2) reported information on the outcomes of interest, and 3) compared treatment outcomes between TB patients with and without HIV co-infection. Studies that focused on patients with latent TB were excluded.

Using the search strings listed in Figure 1, 896 articles were identified and imported into EndNote X9. Of these, 122 duplicates were found through EndNote X9 and were eliminated. Title and abstract screening was performed and abstracts that did not contain all of the words "tuberculosis," "HIV," "children" or some variation of the terms, were also eliminated. When

500 articles remained, they were imported into Covidence. The articles were not imported directly into Covidence because there was a maximum limit of 500 articles.

In Covidence, seventy articles were excluded because they were not scientific studies. Non-scientific studies included individual case reports or guidelines. Fifty-six other articles were omitted because the outcome of interest was not stratified by age. One hundred and twenty-three additional articles were eliminated because they did not include HIV influence on outcomes of interest. Another 226 were excluded because there was not an ability to compare the outcome of HIV co-infected with a control group who had TB disease but no HIV infection. After the series of exclusions, 25 articles remained for analysis. The results of the search and evaluation of the available literature are also summarized in Figure 1.

Data Analysis

When available, point estimates and lower and upper bounds of 95% confidence intervals were extracted from the articles for the favorable treatment outcome, unfavorable treatment outcome and mortality rate values. When point estimate data was not explicitly stated in the articles, raw data was used to calculate this value using OpenEpi software. A random effects meta-analysis model was used to calculate the pooled relative incidence estimates. This model was chosen because it assumes that the gathered estimates are drawn from different populations.[15] I^2 was used to assess for heterogeneity. Funnel plots and the trim and fill method were used to test for influence of smaller studies and symmetry of results. All analyses were performed in Stata 12.1.

Overview of the Available Literature

The data elements extracted from each eligible study included author, year, study design, location, age categorization, outcome definition, sample size, and the relevant results expressed as risk ratios (or similar estimates) along with the corresponding 95% confidence intervals. This information was summarized in Table 1. The publication dates spanned a 23-year period from 1996 through 2018. Eighteen of the publications were based on retrospective cohorts, 6 used data from prospective cohorts and 1 was a case-control study. With respect to geographic distribution 3 studies were conducted in Asia, 20 were from Africa, 1 was from Central America and 1 was from South America.

Results

Qualitative Description of Studies

A retrospective cohort study in Nigeria identified 299 children under 15 who had begun treatment for TB disease between 2010 and 2014.[16] The purpose of the study was to determine mortality rate of the children over time. HIV status was known for 289 of the children. Results of the study showed that children with HIV co-infection were at significantly higher risk of death than children with TB disease in the absence of HIV infection (RR=1.66, 95% CI: 1.02–2.71).

Another retrospective cohort study in Benin was conducted to determine the burden of TB, characteristics and outcomes in children being treated for TB disease in Cotonou.[17] The cohort of interest included 163 children under the age of 15 years old who received treatment between 2009 and 2011. HIV status was known for only 149 of the patients. The number of children with favorable outcomes and unfavorable outcomes (death, loss to follow up, unknown) was reported. Risk ratios were calculated to compare the two measures and it was found that the

number of children with favorable outcomes was significantly greater in the HIV-uninfected group than in the HIV-infected group (RR=0.73, 95% CI: 0.56–0.96). Although death was not measured separately, values were provided so that we were able to calculate risk ratios using Open EPI software. It was found that children with TB/HIV co-infection had 1.73 times the risk of death as compared to children with TB but not infected with HIV (RR=1.73, 95% CI: 0.64-4.71).

A retrospective cohort study was conducted in Nigeria between January 1, 2012 and December 31, 2012.[18] This study examined treatment outcomes of 493 cases of TB disease with known HIV status in children 14 years of age or younger. The authors compared the number of patients who died, experienced favorable and unfavorable treatment outcomes (defaulted, failed treatment and transferred) between HIV positive and HIV negative groups. It was found that there was no significant difference between the groups, with the exception of the mortality category (favorable outcome RR=0.92, 95% CI: 0.82-1.03 and unfavorable outcome RR=1.31, 95% CI: 0.93-1.85). It was found that children with TB/HIV co-infection had 2.89 times the risk of mortality as compared to children with TB but not infected with HIV (RR=2.89, 95% CI: 1.02-2.71).

A retrospective cohort study took place in the Democratic Republic of the Congo between January 2005 and December 2011.[19] This study sought to examine outcomes and the factors related to the outcomes in children admitted to the University Clinics of Kinshasa for TB disease treatment. This study enrolled 283 children 15 years of age or younger, however, HIV status was only known for 72 patients. It was found that although HIV status was related to TB outcomes, this association was not a predictor of unfavorable treatment outcomes including treatment failure, default, transfer or failure to be cured (unfavorable outcome RR=1.55, 95% CI:

0.60-3.97 and favorable outcome RR=0.79, 95% CI: 0.41-1.53). Although mortality was significantly different between the two groups, there was only one death total and the authors warn about the need to interpret these results with caution (RR=928600, 95% CI: 0-13800).

Bobossi-Serengbe and colleagues conducted a retrospective cohort study in the Central African Republic.[20] The files of 284 children treated for TB disease between the ages of 18 months and 15 years during April 1998 and June 2000 were examined. The authors compared favorable TB treatment outcomes, mortality, treatment failure, abandonment and transfer (unfavorable outcomes) between 28 HIV positive patients and 72 HIV negative patients. It was found that favorable TB treatment outcomes were significantly more common in HIV negative patients as compared to HIV positive patients (RR=0.35, 95% CI: 0.15-0.79). Additionally, mortality was also significantly higher for HIV positive patients than for HIV negative patients (RR=2.94, 95% CI: 1.66-5.19). However, when all unfavorable outcomes were combined (death, treatment failure, abandonment and/or transfer) there was not a significant difference between the two groups (RR=0.86 95% CI: 0.41-1.79).

. A retrospective cohort study took place in Kenya in order to assess mortality differences between children with TB disease and HIV and children with TB but not infected with HIV.[21] Patients aged between <1 year and 14 years and were included if they had been treated for TB between October 2006 and September 2007. HIV status was known for 580 of the patients. By calculating risk ratios, it was found that children with HIV were significantly more likely to die than children without HIV (RR 2.3, 95% CI 1.1–5.0).

A retrospective cohort of took place in Brazil to compare socio-demographic and clinical characteristics of children with TB and with and without HIV infection.[22] This study identified 6,091 cases of children under the age of 15 who were being treated for TB between January 2007

and December 2011. HIV status was known for 1263 of the participants. Compared to children with TB and not infected with HIV, patients with TB/HIV co-infection were significantly more likely to die and have unfavorable treatment outcomes (mortality RR 4.89, 95% CI 3.80–6.30 and unfavorable outcomes RR=03.47, 95% CI: 02.95-4.09). Additionally, children with TB/HIV co-infection were significantly less likely to experience favorable treatment outcomes (RR=0.67, 95% CI: 0.63-0.72).

A retrospective cohort in Malawi examined treatment outcomes in children with TB disease.[23] Treatment records between January and December 20012 of the Malawi Ministry of Health were examined and 345 children under the age of 15 with known HIV status were included in the study. It was found that children with TB disease and HIV co-infection were not significantly at higher risk of dying or having unfavorable treatment outcomes as compared to children with TB in the absence of HIV infection (mortality RR=1.47, 95% CI: 0.49-4.41 and unfavorable outcomes RR=1.5, 95% CI: 0.96-2.34).

A retrospective cohort study in Jamaica examined the records of children aged 0-12 years being treated for TB disease between 1999 and 2002.[24] HIV status was known for 24 of the participants, of which, the authors compared mortality in children with TB and HIV co-infection with those not co-infected with HIV. It was found that the number of deaths was significantly greater in HIV co-infected children than in children not infected with HIV (RR= 7.64, 95% CI: 1.11-52.55).

Hailu and colleagues conducted a retrospective cohort study in Ethiopia to examine childhood TB disease treatment outcomes in both HIV positive and HIV negative patients.[25] Records of children 14 years of age or younger who were registered for TB disease treatment between 2007 and 2011 were investigated. Outcomes were grouped as favorable treatment

outcomes (cured/completed treatment) and unfavorable treatment outcomes (died, failed defaulted or transferred out of treatment). It was found that those co-infected with HIV had significantly higher mortality and unfavorable treatment outcomes as compared to those without HIV co-infection (mortality RR=3.41, 95% CI 1.85-6.27 and unfavorable outcome RR = 1.27, 95% CI 0.24-0.0.55). Favorable treatment outcomes were also significantly higher in those without HIV co-infection (RR=0.93, 95% CI 0.87-0.98).

A retrospective cohort in South Africa reviewed records from 2004 to 2008 of children aged 0-17 years diagnosed with multi-drug resistant TB (MDRTB).[26] HIV status was known for 395 of the children. Outcomes examined included favorable treatment outcomes, mortality, failed treatment and lost to follow up (unfavorable treatment outcome). These outcomes were compared between MDRTB in children without HIV infection and MDRTB in children who also had HIV co-infection. It was found that a significantly lower proportion of HIV negative TB cases died as compared to TB cases who were HIV-positive (RR=1.90, 95% CI 1.18-3.09). However, no significant difference was found between the two groups when favorable treatment outcomes and combined unfavorable outcomes were compared (favorable outcome RR=0.89, 95% CI 0.78-1.05 and unfavorable outcome RR = 1.17, 95% CI 0.93-1.48).

A prospective cohort study in India enrolled 223 children less than 5 years of age who were receiving treatment for TB disease.[27] HIV status was known for 210 of these participants. Mortality between August 15, 2010 to March 28, 2012 of children with TB and HIV and only TB were compared. It was found that compared with HIV negative children, HIV positive children had significantly higher risk of mortality (RR=45, 95% CI 5.52-367.1).

Two studies were performed by Jeena and colleagues in South Africa to examine TB disease treatment outcomes in children.[28] The first study was performed prospectively between

1992 and 1994 and examined outcomes in children diagnosed with TB disease between the ages of 8 to 51 months. HIV status was known for 80 children. Compared to children with TB disease and no HIV infection, HIV co-infected children were significantly less likely to experience favorable treatment outcomes and significantly more likely to die (favorable outcome RR=0.68, 95% CI 0.54-0.86 and mortality RR = 1200, 95% CI 1,000 - >1318000). Although these results are informative, we suggest caution be taken when observing the large risk ratio for mortality since the number of children who died over the study period was only 6 total and all of the deaths occurred in children with HIV.

The second study conducted by Jeena and colleagues examined mortality in 101 older children, aged 0-12 years.[29] In contrast to the first study, conducted in 1996, this study was a retrospective study and examined the treatment records of 101 children with known HIV status from January 1998 and December 1999. No significant difference was found when mortality was compared between children with TB/HIV co-infection and those with only TB disease (RR= 1.54, 95% CI: 0.57-4.19).

A prospective study in India compared probability of mortality between children with TB disease and those with TB/HIV co-infection.[30] The children, ages 1 month to 12 years, were followed from May 2000 to August 2003. HIV status was known for 123 of them. It was found that probability of mortality was not significantly different between the two groups of children (RR= 0.53, 95% CI: 0.08-3.43).

A prospective cohort study in Thailand took place between 2005 and 2006.[31] The study included 177 TB disease cases of children aged 0-14 years of whom HIV status was known. It was found that, compared to HIV co-infected children, children with TB disease who did not have HIV infection were significantly less likely to die (RR=8.84, 95% CI: 2.06-38.02).

However, no significant difference was found when favorable and unfavorable outcomes were compared (favorable outcome RR=0.98 95% CI 0.79-1.21 and unfavorable outcome RR = 1.22, 95% CI 0.79- 1.89).

A case-control study in Botswana compared mortality of children less than 15 years of age diagnosed with TB disease.[32] Parents of 187 children with known HIV status who were being treated for TB disease were interviewed to assess risk factors for death during the treatment period of 1998 and 2002. The study found that mortality was not significantly different between children with HIV/TB co-infection as compared to children with TB disease but not infected with HIV (RR= 2.1, 95% CI: 1.00-4.40).

A retrospective cohort study in Nigeria examined 724 records of children with known HIV status being treated for TB disease between January and December 2015.[33] These records included children aged 0 to 14 years. Favorable and unfavorable treatment outcomes for HIV/TB co-infected children were compared to TB disease in children not infected with HIV. After analysis, it was found that HIV co-infected children were less likely to experience favorable TB treatment outcomes and more likely to experience unfavorable treatment outcomes than children with TB disease but no HIV infection (favorable outcome RR=0.84 95% CI 0.74-0.95 and unfavorable outcome RR = 1.92, 95% CI 1.35- 2.73).

A retrospective cohort study in Kenya examined records of 21,696 children with known HIV status being treated for TB disease between 2013 and 2015.[34] Children in the study were less than or equal to 14 years of age. After comparison of TB disease in HIV co-infected children and TB disease in children with no HIV infection, it was found that HIV-infected children were at significantly higher risk for death than children without HIV infection (RR= 3.61, 95% CI: 3.2-4.09).

A retrospective cohort study in South Africa examined mortality and unfavorable treatment outcomes (treatment failure, death, moved, transferred, lost to follow-up) in children aged less than 15 years old.[35] The sample consisted of 16,305 children with known HIV status who were being treated for TB disease between 2005 and 2012. Compared to children with TB disease and no HIV infection, children with HIV/TB co-infection were significantly more likely to die and have unfavorable treatment outcomes (mortality RR= 6.85, 95% CI: 4.6-10.19 and unfavorable outcome RR= 2.01, 95% CI: 1.81-2.23).

A prospective cohort study in South Africa followed the outcomes of children being treated for TB disease between 1998 and 1999.[36] Children aged from 0 to 12 years and were evaluated based on favorable treatment outcomes or mortality during the study period. HIV status was known for 150 of the children. It was found that, compared to children with TB disease who were not infected with HIV, those with both TB disease and HIV co-infection were significantly less likely to experience favorable treatment outcomes and more likely to die by the end of the study period (favorable outcome RR= 0.35 95% CI: 0.15-0.82 and mortality RR= 9.5, 95% CI: 2.01-45.02).

A prospective cohort study in Ethiopia followed children being treated for TB disease between 1995 and 1997.[37] The children were between the ages of 0 and 14 years and HIV status was known for 517 of them. The study compared favorable treatment outcomes, unfavorable treatment outcomes and death rates between children with TB disease but not infected with HIV and those with both TB disease and HIV infection. It was found that children with TB disease but not infected with HIV were significantly more likely to experience favorable treatment outcomes and significantly less likely to die or experience unfavorable treatment outcomes as compared to HIV co-infected children (favorable outcome RR= 0.76, 95% CI: 0.60-0.96,

mortality RR= 6.70, 95% CI: 4.07-11.02 and unfavorable outcome RR=1.77, 95% CI: 1.31-2.37).

A retrospective cohort study in South Africa compared TB disease treatment outcomes of children diagnosed with TB disease and those diagnosed with both TB disease and HIV.[38] The children were all under the age of 15 and were in treatment for TB disease between January 2003 to December 2008. HIV status was known for 72 of the participants. It was found that children with HIV co-infection were not significantly more likely to die than those with TB disease but not infected with HIV (RR= 2.16 95% CI: 0.74-6.36). In contrast, unfavorable treatment outcomes were significantly more likely for children with HIV/TB co-infection than for children with TB disease and not infected with HIV (unfavorable outcome RR= 10.9, 95% CI: 1.17-101.00).

A retrospective cohort study in the Western Cape of Africa looked at treatment outcomes of children both co-infected with HIV and TB disease and those diagnosed with only TB disease.[39] Records from January 2000 and December 2001 of 138 children under the age of 15 with known HIV status were examined. It was found that HIV co-infected children were significantly more likely to die and experience unfavorable treatment outcomes than children with TB disease in the absence of HIV infection (mortality RR= 6.6, 95% CI: 1.4-31.51 and unfavorable outcome RR= 2.65, 95% CI: 1.65-4.35). This significant difference was also seen when favorable treatment outcomes were compared, with HIV co-infected children being less like less likely to experience favorable outcomes (favorable outcome RR= 0.46, 95% CI: 0.30-0.72).

A retrospective cohort in Ethiopia examined treatment outcomes in 291 children with known HIV status being treated for TB disease between 2009 and 2013.[40] The children were all

14 years of age, or younger. The authors compared favorable treatment outcomes to unfavorable outcomes (transferred out, default, death, failure, unknown outcome) in children with TB disease and not infected with HIV to those with TB disease and co-infected with HIV. It was found that children who were HIV negative showed significantly higher rate of favorable treatment outcomes and lower rates of unfavorable treatment outcomes as compared to the HIV positive patients (favorable outcome RR=0.75, 95% CI: 0.65-0.87 and unfavorable outcome RR=4.71, 95% CI: 2.52-8.79).

Meta-analysis for Favorable Treatment Outcomes

The meta-analysis for favorable treatment outcomes included 14 studies (Figure 2). The summary risk ratio of all included studies was 0.77 (95% CI: 0.70- 0.86) with high degree of heterogeneity (p=0.000, I^2=83.6%). These results show that children with TB disease who are not infected with HIV are significantly more likely to experience favorable treatment outcomes than children with both TB disease and HIV co-infection. Funnel plots and the trim and fill method used to test for influence of smaller studies and symmetry of results did not suggest the presence of publication bias (Figures 3 & 4).

Meta-analysis for Overall Mortality

The meta-analysis for overall mortality included 24 studies (Figure 5). The summary risk ratio of all included studies was 3.26 (95% CI: 2.57- 4.14) with fairly high degree of heterogeneity (p=0.000, I2=67.3%). These results show that children with TB disease who are not infected with HIV are significantly less likely to die than children with both TB disease and HIV co-

infection. Funnel plots and the trim and fill method used to test for influence of smaller studies and symmetry of results did not suggest the presence of publication bias (Figures 6 & 7).

Meta-analysis for Unfavorable Treatment Outcomes

The meta-analysis for unfavorable treatment outcomes included 15 studies (Figure 8) . The summary risk ratio of all included studies was 1.77 (95% CI: 1.40- 2.24) with high degree of heterogeneity (p=0.000, I^2=86.2%). These results show that children with TB disease who are not infected with HIV are significantly less likely to experience unfavorable treatment outcomes than children with both TB disease and HIV co-infection. Funnel plots and the trim and fill method used to test for influence of smaller studies and symmetry of results did not suggest the presence of publication bias (Figures 9 & 10).

Discussion

Summary of evidence

In the current meta-analysis, we examined whether TB disease treatment outcomes and mortality rates differed between children with TB disease without evidence of HIV infection and children with both TB disease and HIV co-infection. The results of analysis showed significant differences between the groups in all categories. Children with TB disease and HIV co-infection were less likely to have favorable treatment outcomes and more likely to die and/or have unfavorable treatment outcomes than children with TB disease in the absence of HIV infection.

This finding is consistent with past evidence in adults, and other observations. In adults, studies have examined the impact of TB/HIV co-infection and many have concurred that outcomes are worse when co-infection is present.[4-7, 41] Although, when compared to adults, TB

presents differently in children, the similarity of the TB treatment outcomes findings are consistent and reinforced by this systematic review and meta-analysis.

Strengths and Weaknesses

To our knowledge, this is the first meta-analysis to examine treatment outcomes in children with TB disease and HIV co-infection as compared to children with TB disease in the absence of HIV infection. Another strength of the study is the exhaustive nature of the literature search. Several databases were reviewed and hundreds of studies were examined for verification. Adding to the strengths of this study is our explicit examination of publication bias, and finding that bias did not impact results. Finally, with the exception of one study, all of the included articles were either prospective or retrospective comparative studies. These are authoritative approaches to answer the scientific question of interest.

Despite the strengths of these analyses, there are at least three weaknesses that must be acknowledged. First, the measure of unfavorable TB treatment outcomes was not consistently defined in the various studies. For example, some studies defined the measure as including patients who died and either defaulted, transferred out or did not complete treatment, whereas other studies included only all of these measures in addition to death. In order to include as many articles as possible, the category of unfavorable treatment outcomes was collapsed down to include the widest definitions given by the studies. In doing so, we lost the ability to make comparisons between separate unfavorable outcomes.

A second limitation of this study is the large and non-systematic age range of participants. When reporting on TB morbidity and mortality, the World Health Organization typically defines children as individuals aged 0-14 years.[3] Ideally, this review would have been

limited to children in this same age group. However, in an effort to include as many studies as possible, this age range was extended from 0 to 17 years of age. Differences in both age and measure of outcomes might explain the high rates of heterogeneity in the studies. Third, the exhaustive literature review was limited to publications in English and may thus have excluded relevant publications in other languages.

Conclusion

In summary, we conclude that treatment outcomes are worse for children with TB disease and HIV co-infection than for children with TB in the absence of HIV co-infection. Meta-analysis of the reviewed articles showed statistically significant differences in all three of the examined categories of favorable treatment outcomes, death rate, and unfavorable treatment outcomes. None of the studies that we reviewed found that children with TB disease and HIV co-infection have better outcomes than children with TB but no HIV co-infection, leading us to conclude that HIV co-infection has either a negative or null impact on treatment outcomes. None of these outcomes assessed the predictably beneficial role of antiretroviral therapy (ART) for children co-infected with HIV.

Future Directions

Based on the findings and limitations of the current review, several next steps can be recommended. First, additional studies which rigorously compare specific TB disease treatment outcomes in HIV co-infected children with TB treatment outcomes in children without HIV infection are warranted. Second, another direction of future research should include similar assessments, taking into consideration presently-recommended practices to provide ART to all

children co-infected with HIV, and thus explore the additive effect of TB disease treatment with ART on outcomes in HIV-infected children. Finally, the degree of how much worse TB treatment outcomes experienced by HIV co-infected children is not clear and deserving of future attention.

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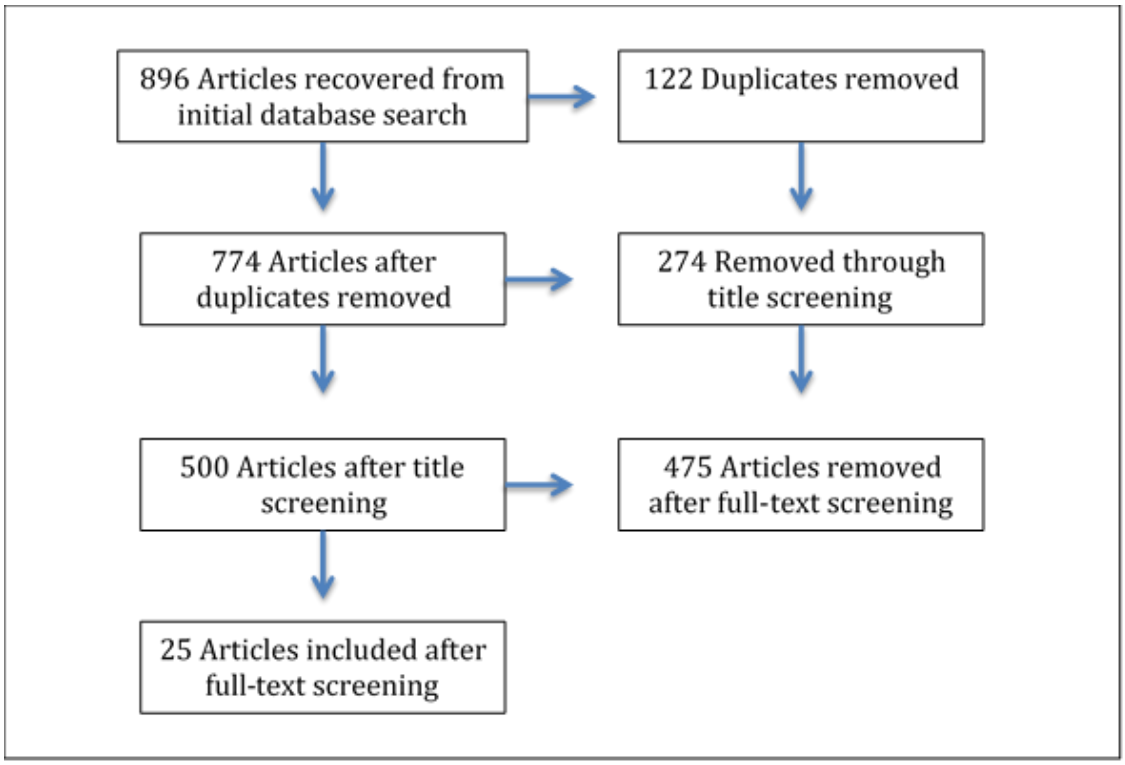
Tables and Figures

Figure 1: Flow chart of the literature search and retrieval



Search Terms

Pubmed search string:

(((((HIV OR HIV/AIDS OR human immunodeficiency virus)) AND (TB OR Tuberculosis)) AND (coinfection OR co-infection)) AND child*) AND outcome*

Embase search string:

('tb'/exp OR tb) AND ('hiv'/exp OR hiv) AND ('coinfection'/exp OR coinfection) AND in AND ('children'/exp OR children)

Cabi search string:

(((((HIV OR HIV/AIDS OR human immunodeficiency virus)) AND (TB OR Tuberculosis)) AND (coinfection OR co-infection)) AND child*) AND outcome*

Table 1: Summary characteristics of studies included in review

Study ID (Author, Year)	Study Design	Location	Age Division	TB Treatment Outcome(s): Favorable, Unfavorable Outcomes or Death	Sample Size	TB treatment Outcome by HIV infection status
Adamu et al., 2017	Retrospective cohort	Nigeria	<15 years	Death	100 HIV+ 189 HIV-	42 (42%) HIV+ died 43 (21.6%) HIV- died
Ade et al., 2013	Retrospective cohort	Benin	<5 years 5-14 years	Favorable Death Unfavorable	45 HIV + 104 HIV -	26 (58%) HIV + favorable 82 (79%) HIV - favorable 6 (13%) HIV + died 8 (8%) HIV - died 19 HIV+ unfavorable 22 HIV- unfavorable
Adebayo et al., 2016	Retrospective cohort	Nigeria	0-14 years	Favorable Death Unfavorable	143 HIV + 350 HIV -	105 (73.4%) of HIV + favorable 279 (78%) of HIV- favorable 16 (11.2%) of HIV + died 14 (4.0%) of HIV- died 38 of HIV+ unfavorable 71 of HIV- unfavorable

Aketi et al., 2016	Retrospective cohort	Democratic Republic of the Congo	≤15 years	Favorable Death Unfavorable	7 HIV + 65 HIV -	4 HIV + favorable 47 HIV - favorable 1 (100%) HIV+ died 0 (0%) HIV- died 3 HIV + unfavorable 18 HIV- unfavorable
Bobossi-Serengbe, 2005	Retrospective cohort	Central African Republic	18 months-15 years	Favorable Death Unfavorable	28 HIV + 72 HIV -	5 (17.9%) HIV + favorable 37 (51.4%) HIV - favorable 16 (57.1%) HIV + died 14 (19.4%) HIV - died 23 HIV + unfavorable 35 HIV- unfavorable
Cavanaugh et al., 2011	Retrospective cohort	Kenya	<1 year 1-4 years 5-14 years	Death	323 HIV+ 257 HIV-	25/323 (8%) HIV+ died 9/257 (4%) HIV- died
dos Santos Dias et al., 2015	Retrospective cohort	Brazil	<14 years	Favorable Death Unfavorable	780 HIV + 5311 HIV -	411 HIV + favorable 4174 HIV - favorable 94 HIV + died 131 HIV - died 180 HIV+ unfavorable 353 HIV- unfavorable
Flick et al., 2016	Retrospective cohort	Malawi	<15 years	Death Unfavorable	226 HIV+ 464 HIV-	No individual population information provided, only odds ratio

Geoghagen et al., 2004	Retrospective cohort	Jamaica	<12 years	Death	11 HIV + 12 HIV -	(7/23) 29.2% HIV+ died (1/23) 4.2% HIV - died
Hailu et al., 2014	Retrospective cohort	Ethiopia	0-4 years 5-9 years 10-14 years	Favorable Death Unfavorable	326 HIV+ 909 HIV-	266 HIV + favorable 801HIV- favorable 22 HIV + died 18 HIV- died 49 HIV+ unfavorable 108 HIV- unfavorable
Hall et al., 2017	Retrospective Cohort	South Africa	≤17 years	Favorable Death Unfavorable	238 HIV + 185 HIV -	131 HIV+ favorable 114 HIV- favorable 49 HIV + died 20 HIV - died 107 HIV+ unfavorable 71 HIV- unfavorable
Jain et al., 2013	Prospective cohort	India	≤ 5 years	Death	21 HIV+ 189 HIV-	5/21 (24%) HIV+ died 1/189 (1%) HIV- died

Jeena et al., 1996	Prospective Cohort	South Africa	8 to 51 months	Favorable Death	40 HIV+ 40 HIV -	26 (65%) HIV+ favorable 38 (95%) HIV- favorable 6 (15%) HIV+ died 0 (0%) HIV- died
Jeena et al., 2002	Retrospective cohort	South Africa	0-12 years	Death	57 HIV+ 44 HIV -	10 (18%) HIV + died 5 (11%) HIV- died
Karande et al, 2005	Prospective cohort	India	≤12 years	Death	8 HIV+ 115 HIV-	1 HIV+ died 27 HIV- died
Lolekha et al., 2008	Prospective cohort	Thailand	<15 years	Favorable Death Unfavorable	75 HIV+ 102 HIV-	49 HIV+ favorable 68 HIV- favorable 13 HIV+ died 2 HIV- died 26 HIV + unfavorable 29 HIV- unfavorable
Oeltmann et al., 2008	Case control	Botswana	<15 years	Death	87 HIV + 70 HIV -	28 (31%) HIV + died 13 (14%) HIV - died
Ogbudebe et al., 2018	Retrospective cohort	Nigeria	0-14 years old	Favorable Unfavorable	108 HIV+ 616 HIV-	77 (71.3%) HIV+ favorable 524 (85.1%) HIV- favorable 31 (28.7%) HIV+ unfavorable 92 (14.9%) HIV- unfavorable

Onyango et al., 2018	Retrospective cohort	Kenya	≤14 years	Death	5991 HIV + 15,705 HIV -	572 (9.5%) HIV + died 415 (3%) HIV - died
Osman et al., 2017	Retrospective cohort	South Africa	<15 years	Death Unfavorable	3143 HIV+ 13162 HIV-	78 (2.7%) HIV+ died 41 (0.3%) HIV- died 689 (21.9%) HIV+ unfavorable 1463 (11.1%) HIV- unfavorable
Oud-Alblas et al., 2002	Prospective cohort	South Africa	0-12 years	Favorable Died	36 HIV+ 114 HIV-	5(14%) HIV+ favorable 45 (39%) HIV- favorable 6 (17%) HIV+ died 2 (2%) HIV- died
Palme et al., 2002	Prospective cohort	Ethiopia	0-14 years	Favorable Treatment failure Death	58 HIV+ 459 HIV-	32 (55%) HIV+ favorable 335(73%) HIV- favorable 22 (38%) HIV+ died 26 (6%) HIV- died 29 HIV+ unfavorable 130 HIV- unfavorable

Seddon et al., 2012	Retrospective cohort	South Africa	<15 years	Death Unfavorable	29 HIV+ 42 HIV-	7 HIV+ died 1 HIV- died 10 HIV+ unfavorable 7 HIV- unfavorable
Soeters et al., 2005	Retrospective cohort	Western Cape	<15 years	Favorable Death Unfavorable	43 HIV+ 95 HIV-	14 HIV+ favorable 67 HIV- favorable 6 HIV+ died 2 HIV- died 24 HIV + unfavorable 20 HIV - unfavorable
Tilahun et al., 2016	Retrospective cohort	Ethiopia	≤14 years	Favorable Death Unfavorable	82 (28.2%) HIV + 209 (71.8%) HIV - 200 (40.7%) Unknown	58 (70.7%) HIV + favorable 196 (93.8%) HIV - favorable 0 (0%) HIV + died 0 (0%) HIV - died 24 HIV + unfavorable 13 HIV - unfavorable

Figure 2: Forest plot of meta-analysis for favorable treatment outcomes

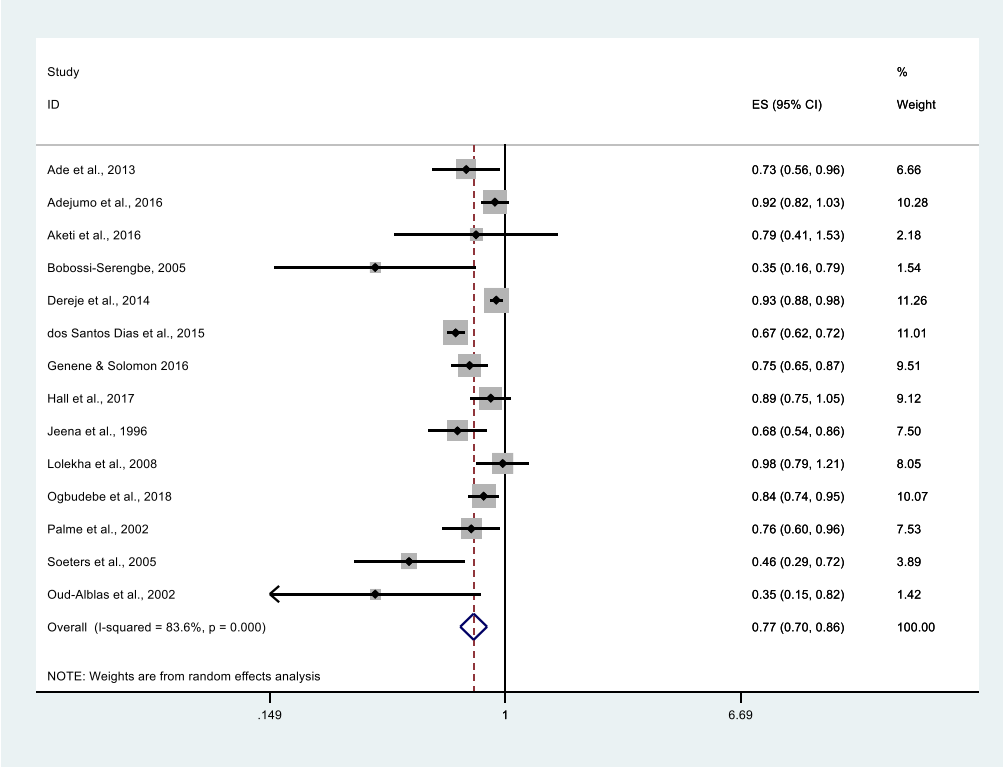


Figure 3: Funnel plot test for heterogeneity favorable treatment outcomes

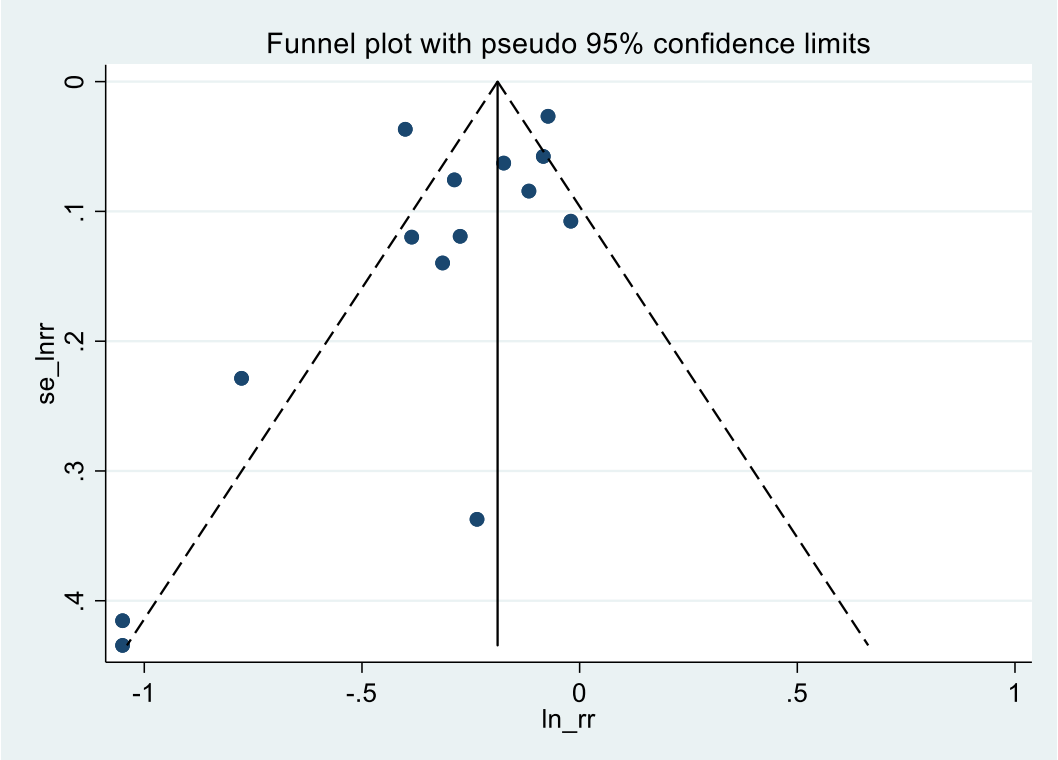


Figure 4: Funnel plot trim and fill test for favorable treatment outcomes

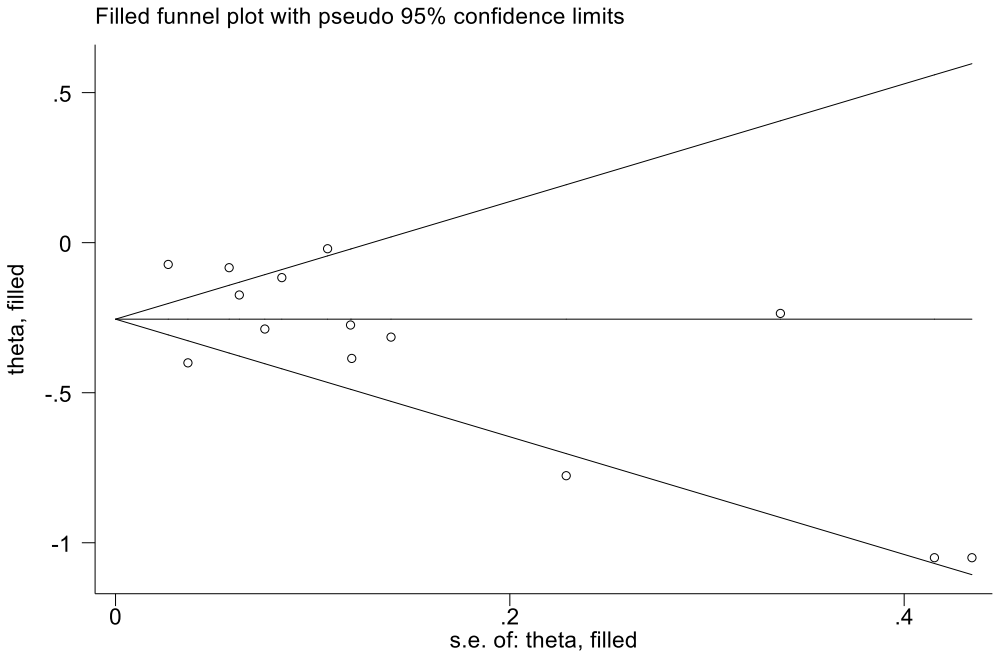


Figure 5: Forest plot of meta-analysis of overall mortality

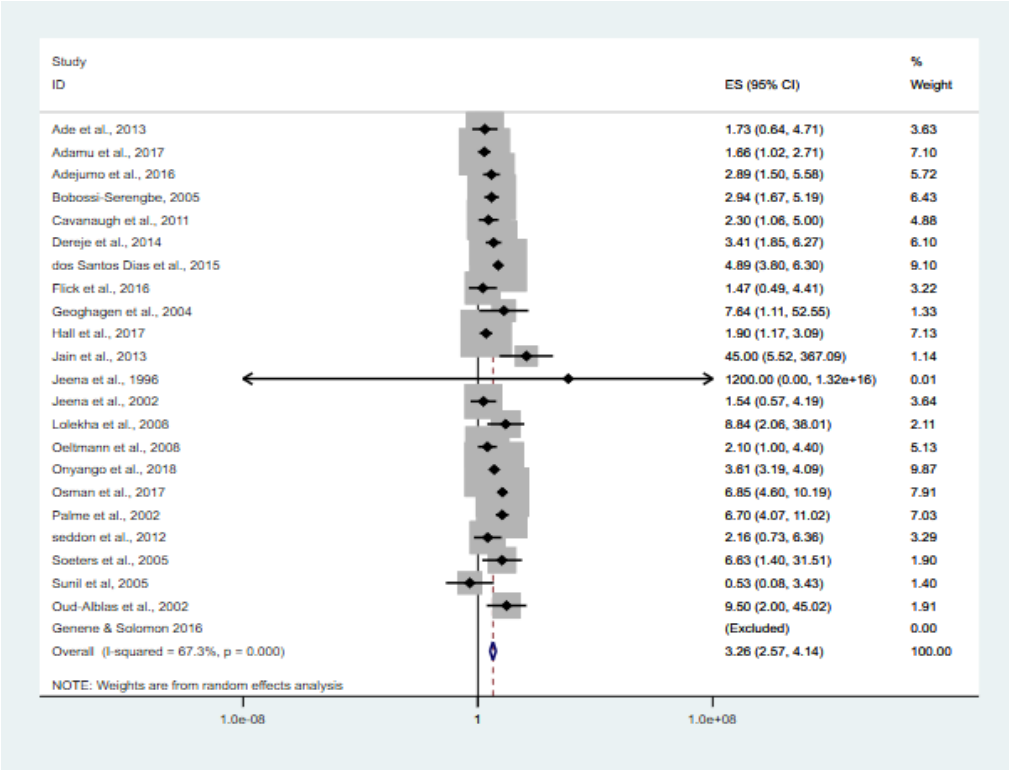


Figure 6: Funnel plot test for heterogeneity overall mortality

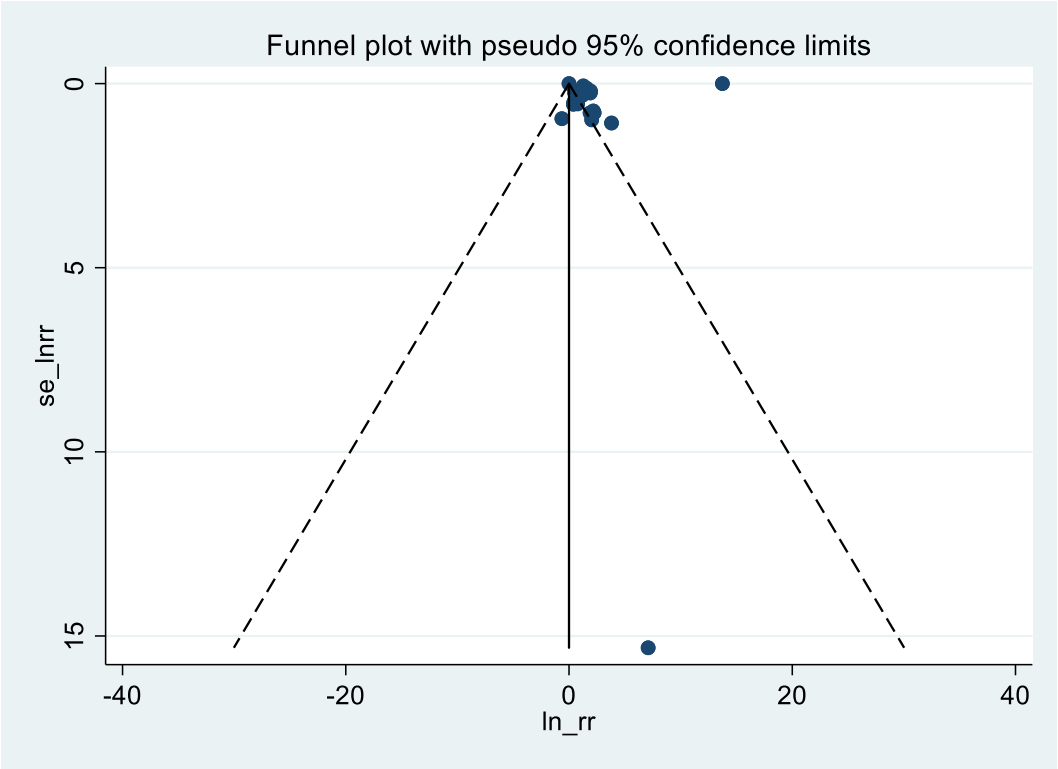


Figure 7: Funnel plot trim and fill test for overall mortality

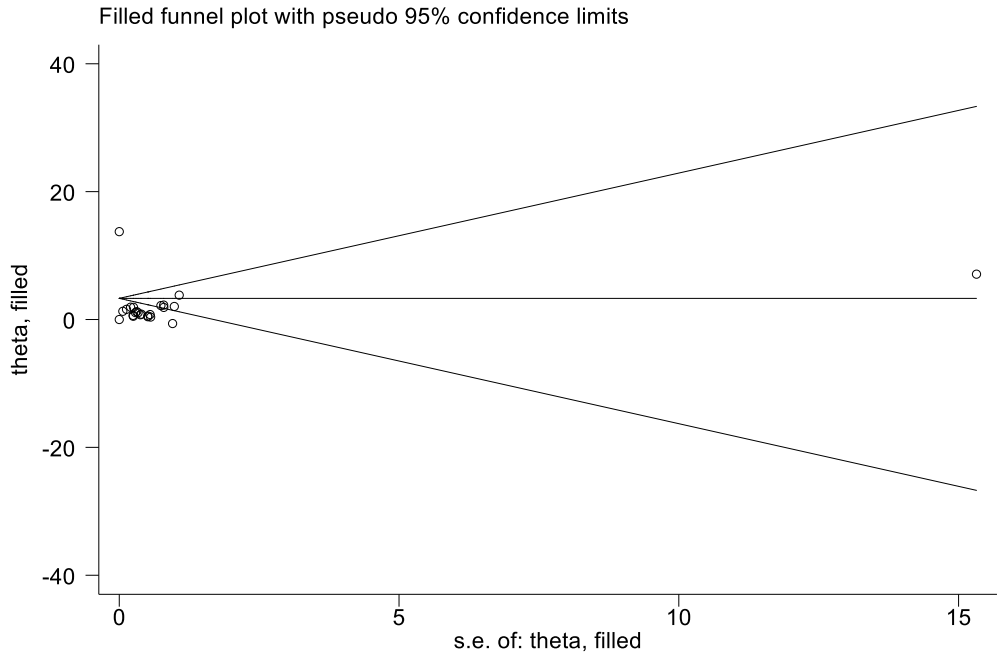


Figure 8: Forest plot of meta-analysis for unfavorable treatment outcomes

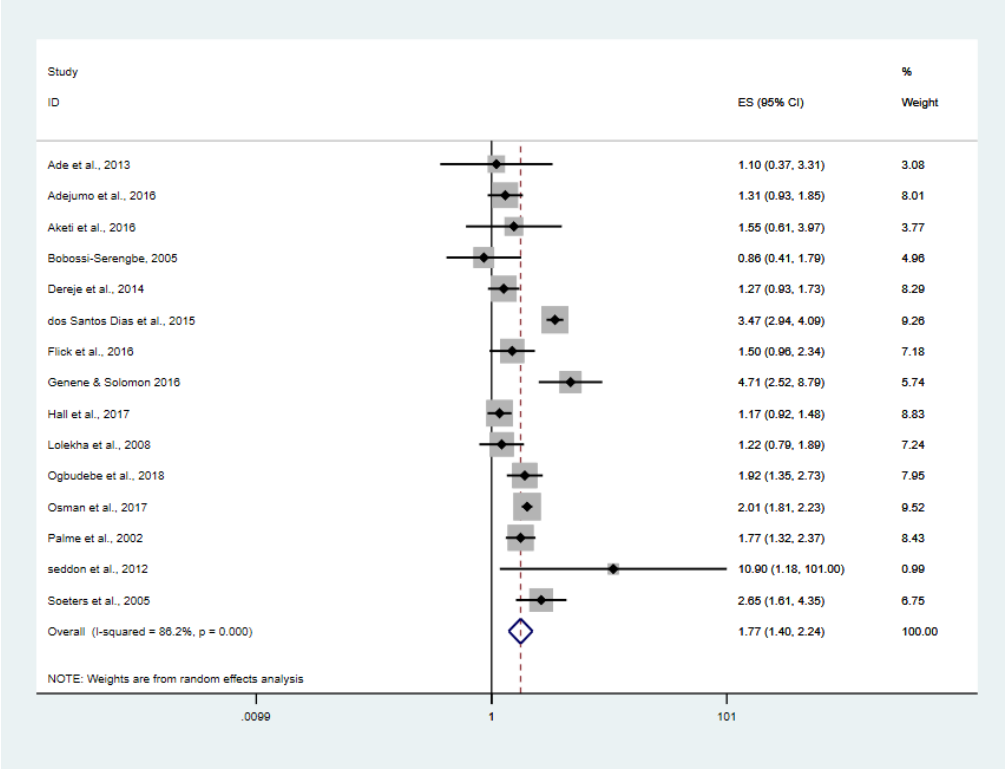


Figure 9: Funnel plot test for heterogeneity for unfavorable treatment outcomes

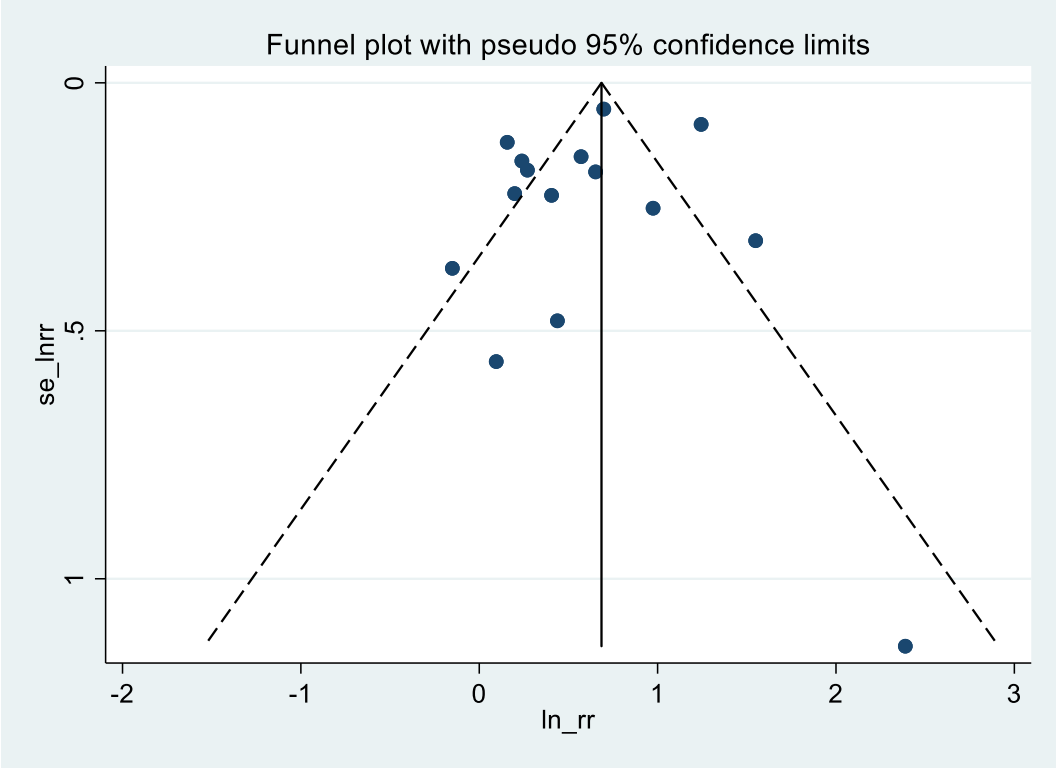


Figure 10: Funnel plot trim and fill test for unfavorable treatment outcomes