

Tuberculosis Treatment Outcomes Among Children in Ethiopia: Systematic Review and Meta Analysis

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Abstract

Background: Tuberculosis (TB) in children is increasingly recognized as a significant public health problem, and as an important component of the total global burden of tuberculosis. Tuberculosis among Ethiopian children is highly prevalent due to poor socio-economic conditions, malnutrition, over-crowding, HIV co-infection and high prevalence of TB in adult contacts. The World Health Organization (WHO) recommends that children with TB should be treated within the National TB Programmes (NTP) and notified through their routine reporting systems. Although with appropriate treatment 95% of children with PTB and non-severe EPTB could be treated successfully their outcome is largely unknown in developing countries including Ethiopia.

Methods: We identified a total of 1138 original articles from the initial computer-based search in PubMed, Hinari, Google Scholar until May 20, 2017, and contacting authors and experts in the field. Of these, 64 full-text studies were eligible for review and 28 articles were used for meta-analysis, including a total study population of 10,929 patients from 7 regions of the country, namely Addis Ababa, Amhara, Afar, Gambella, Oromia, South Nations and Nationalities people and Tigray. All of the studies were published in English, with study populations size varying from 32 to 2381, and undertaken between 2009 and 2017.

Results: The pooled treatment success rate was 85% (CI: 82%-88%) with pooled cure and treatment completed rate of 8% (CI: 6%-11%) and 80% (CI: 76%-85%), respectively. The pooled unsuccessful treatment rate, lost to follow-up rate and death rate were 15% (CI: 12%-18%), 10% (CI: 7%-12%) and 6% (CI: 4%-7%), respectively.

Conclusion: The overall treatment success rate among children was similar with the general population. Close follow up is required for better outcome.

Key Words: Tuberculosis; Children; Treatment outcome

Abbreviations

CI: Confidence Interval; DOTS: Directly Observed Short Course Therapy; EPTB: Extrapulmonary Tuberculosis; HIV: Human Immuno Virus; MDR: Multi Drug Resistance; NTP: National Tuberculosis Program; PTB: Pulmonary Tuberculosis; SNNP: South Nations Nationalities Peoples; TB: Tuberculosis; WHO: World Health Organizations

Background

Tuberculosis (TB) is one of the major public health problems globally [1]. Tuberculosis in children is significant component of the global burden of tuberculosis [2]. In 2016, an estimated 10.4 million people fell ill with TB in 2016: 90% were adults, 65% were male, 10% were people living with HIV (74% in Africa) and 56% were in five countries. Globally, children (aged <15 years) accounted for 6.9% of the new TB cases that were notified in 2016. Of these 1 million new tuberculosis cases occurred in children [3-6]. It is estimated that about 10% of new TB cases occur in children, however, this proportion varies with the prevalence of TB in adults ranging from 3% in low-burden countries to 20-40% in high-burden countries [1, 3]. Tuberculosis among children is much more prevalent in developing countries due to poor socio-economic conditions, malnutrition, over-crowding, HIV co-infection and high prevalence of TB in adult contacts [7]. Despite the fact that TB is the cause of significant childhood mortality and morbidity, childhood TB remains neglected for various reasons like, the highest priority, however, has been given to infectious TB cases (mostly of adults), the difficulty in diagnosing Pulmonary Tuberculosis (PTB), the unknown outcomes of children with TB, the lack of scientific studies on childhood TB, and the dogma that childhood TB is not important in TB control [1, 7, 8].

Moreover, children in TB-endemic areas suffer severe TB related morbidity and mortality, and a large proportion of cases are diagnosed solely on the basis of medical history and clinical examination. In Ethiopia, childhood TB is still a major cause of hospital admission and death [8]. TB is the main cause of hospital death in Ethiopia, and accounts 15,917 new TB cases among children <15 years old [6, 9]. The outcome of children with TB, however, is largely unknown, as the majority has smear-

negative or EPTB [6]. In Ethiopia, one of the 22 high TB burden countries, TB is the second leading cause of death. It is estimated that children contribute to 16.1% of the national TB burden [1]). Because the routine diagnostic test for TB is smear microscopy, correct diagnosis of TB is difficult among the majority of children especially the young since either they do not produce sputum or have paucibillary sputum. Thus, diagnosis in these patients heavily depends on clinical history (suggestive symptoms, poor response to a course of antibiotics, contact to known PTB patients) and physical examination including growth assessment and chest x-ray [2].

Correct treatment of tuberculosis aims at curing the patient, interrupting transmission of tuberculosis to other persons and preventing bacilli from becoming drug resistant. Treatment outcome results serve as a proxy of the quality of TB treatment provided by a health care system. Ideally, treatment outcome in all patients should be routinely monitored by the epidemiological surveillance system [10].

In Ethiopia, a standardized TB prevention and control program incorporating DOTS was started as a pilot in 1992, at Arsi zone in Oromia region. The DOTS strategy has been subsequently scaled up and implemented at a national level. Currently, the DOTS geographic coverage has reached 90%, whereas the DOTS health facility coverage is 75%. Understanding the specific reasons for unsuccessful outcomes under the DOTS program is important in order to improve treatment strategy [11]. The purpose of this review was to assess and summarize the available evidence of treatment outcomes in children in the Ethiopian settings and to assess existing evidence for the treatment of MDR tuberculosis in children.

Methods

Study selection

Studies obtained from the literature search were checked by title and citation. References from the selected studies were also assessed to ensure that no relevant studies were omitted. Studies were required to meet the following inclusion criteria: firstly, studies involving children under age of 15 were considered eligible and secondly, treatment outcome definitions specified by Mycobacterium culture or mycobacterial acid fast smear endpoints (e.g., "cured" defined as at least five consecutive negative cultures during the last 12 months of treatment), and outcomes reported according to the WHO classification of success (including cure or treatment completion), failure, Lost to follow-up (treatment interruption), and death.

Studies were excluded from the analysis for any of the following reasons: involving comments, editorial reviews, and articles focusing only on adult population; dealing with a mycobacterium other than Mycobacterium tuberculosis; focusing on MDR treatment; did not specify strategy; duplicate publications of the same study. The selection of articles for review was done in three stages: looking at the titles alone, then title and abstracts, and full-text articles by (WB and BT).

Assessment of methodological quality

Studies were assessed for quality and the high-quality studies were then analyzed. The studies were considered high quality if they reported outcomes on at least 10 patients and reported that less than 20% of patients were lost to follow up. When study populations overlapped, we included the more recent and larger study population in the analysis. The quality of the included studies was assessed using a check list adopted from Newcastle-Ottawa quality assessment scale [12].

Data extraction

Data abstraction was performed by two reviewers (WB and BT) using a standardized abstraction form. When there was disagreement, the relevant paper was reviewed and differences were resolved by discussion and consensus.

Statistical analysis

Data analysis was performed using Stata version 14.0 (Stata Corp., College Station, Texas, USA). The detail description of the original studies was presented in a table and forest plot. The pooled estimate of TB treatment outcome in children was determined using the DerSimonian-Laird for random effects meta-analysis (random effects model), and was measured as proportions of treatment outcomes with 95% confidence intervals (CIs). A subgroup analysis was performed by region. Statistical heterogeneity and exploration of publication bias were assessed by the Begg's rank correlation test and Egger weighted regression test and $p < 0.05$ was considered as indicative of statistically significant publication bias. Statistical heterogeneity between studies was evaluated using the Cochran's Q test, which shows the amount between study heterogeneity and I² statistic. The I² statistic is a measure of the percentage of variability (inconsistency) between studies that happened due to by chance as conflicted to the actual difference between study populations. Therefore, the presence of statistical heterogeneity was tested using Cochran's Q test ($P < 0.10$ indicative of statistically significant heterogeneity) and I² test (values of 25, 50 and 75% were considered to represent low, medium, and high heterogeneity, respectively).

Results

A total of 1137 studies have been identified from PubMed, Hinari, and Google Scholar electronic databases. One additional article was identified through contacting the Author. Of these, 1109 studies were excluded: 576 were duplicated studies and 497 were excluded during title and abstract screening for relevance of the literatures for this review. Therefore, 64 studies were eligible for full text screening. After a careful screening of the full text articles, 36 studies were excluded as for 10 studies age based treatment outcome was not reported, for 16 studies treatment outcome of the cases was not indicated, the remaining studies were disregarded either reported among adult TB patients or done outside Ethiopia [13-15].

The remaining 29 articles were subjected for the qualitative analysis and 28 articles were used for meta-analysis. A total of

10929 patients from 7 regions of the country, namely Addis Ababa, Amhara, Afar, Gambella, Oromia, South nations and nationalities people and Tigray were included in the meta-analysis. Out of the studies included in the Meta analysis, 26 studies were used for treatment success rate and unsuccessful treatment rate while 16, 20, 19, 23 studies were used for cure rate, treatment completed, Lost to follow-up and death rates analysis, respectively (Figure 1).

Since these studies were carried out in various regions of the country, factors such as type of sample patients, method of case ascertainment, sample size difference and age differences are known to influence the outcome of tuberculosis treatment outcome. It is therefore, not surprising that the studies conducted over a wide geographical area involving different regions of the country and conducted at different time points were heterogeneous.

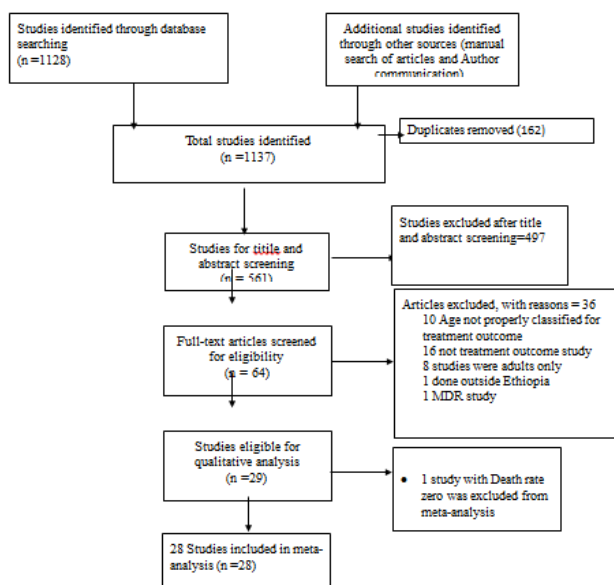


Figure 1: Flow chart showing the included studies

Description of the studies included in the review

It shows the characteristics of the studies included in this review. All of the studies included in the systemic review and meta-analysis were observational studies. All of the studies were published in English, with study populations varying from 32 to 2381 and undertaken between 2009 and 2017 with the data collection period from 1997 to 2016 [16,17-19].

Tsnireatment outcomes

The pooled treatment Success rate was 85% (82%-88%) with pooled cure and treatment completed rate of 8% (6%-10%) and 80% (76%-85%) respectively. The pooled unsuccessful treatment rate was 15% , of whom 10% of cases were Lost to follow-up and 6% were deaths. The overall cure rate of children treated for all forms of tuberculosis was 8% (6%-11%). In the forest plot above the significant heterogeneity may be due to the sample size differences among the studies as clearly shown in the confidence interval gap of some of the studies [20-22].

As indicated in the above forest plot the pooled treatment completed rate was 80%(76%-85%). The pooled unsuccessful treatment rate (Lost to follow-up, death, failed) was higher in Amhara region 20%(10%-30%) whereas the lowest unsuccessful treatment rate was reported in Tigray region 5% (3%-6%).

Discussion

Ethiopia is among the 30 High TB, HIV and MDR-TB Burden Countries, with annual estimated TB incidence of 177/100,000 populations rate of 25 per 100,000 populations for 2016. Among the notified TB cases in 2016, 2.7% of new TB cases and that on 14% of the retreated TB cases were estimated to harbor drug resistant TB. In 2016, Ethiopia notified 125,836 new TB cases. Cases were reported among children aged under 100 (12%) 15 years while the 8% of the TB cases were also HIV co-infected. In the same calendar year, the program diagnosed 706 drug-resistant TB cases and put on second line treatment[15]. The Country follows passive case finding strategy and children infected with tuberculosis are treated based on the DOTs program.

Although the treatment success rate of properly treated children is better than those of adult populations. This meta-analysis showed that the pooled treatment Success rate (85%) was similar with the treatment success rate of the general population of the country (84%), global (83%) (3) and the general population treated for tuberculosis in Ethiopia from 2003 to 2016. However, the result was lower than the target set by the Federal ministry of health of Ethiopia in its health sector transformation plan for the year 2017/18 (95%). The pooled treatment success rate of this meta-analysis was lower than the treatment success rate (89.5%) outcomes of children treated for tuberculosis in cape town, South Africa.

Thus, better attention should be given to enhance and strengthen the DOTs program among children in the country. The pooled Cure rate was 8% which is by far lower than the treatment completed rate which is 80%. This pooled cure rate was lower than the pooled cure rate of general population treated for tuberculosis in Ethiopia (33.9%) and higher than the pooled success full treatment outcome among children treated for Multidrug resistance tuberculosis 81.67%. It is the best indicator of the impact of a tuberculosis control program among children. The low proportion of cure rate in this review clearly indicates the potential transmission of the disease in the population even from patients who are on anti TB treatment. However, bacteriological (smear microscopy and/or culture) confirmation is required to verify the exact treatment outcome, which is rarely used in Ethiopia especially for children due the paucibillary nature of sputum production among children as well as limited availability of culture facilities in tuberculosis treatment centers. Therefore, this pooled cure rate may underestimate the treatment conversion rate and impact of tuberculosis control efforts in the country.

The pooled unsuccessful treatment rate which includes (Lost to follow-up rate, treatment failure rate and death rate) was

15%. Of these outcomes treatment failure and Lost to follow-up rates accounted more than 10% of the total treated case are risk factors for the development of MDR tuberculosis and may lead to serious challenge to the tuberculosis control program in the country. Therefore, attention should be paid at these outcomes.

Based on the current systematic review and meta-analysis the pooled death rate (6%) was lower than the pooled death rate of children with tuberculosis diseases both in pre and post treatment era (11.24%). However, the pooled death rate was lower than the pooled death rate (0.9%) after tuberculosis treatment era in the same systematic and meta-analysis finding. The pooled death rate of this meta-analysis is comparable with the meta-analysis pooled result among children treated for tuberculosis infection (5.9%).

The Six percent death rate among children who were under the DOTs program point out that the DOTS program as well as the overall childhood TB management system should be seriously evaluated since there is a gap between the health sector transformation plan and actual performance of successful treatment out comes among tuberculosis infection treated patients in the country.

Limitation of the study

All studies included in this review were observational data for treatment outcomes from tuberculosis treatment center registration book. This may affect the quality of the evidence.

Since there was no separate documentation for new and retreatment cases we were not able to do subgroup analysis for new and previously treated TB cases. Presence of high heterogeneity across studies was another limitation of this review which might be due to sample size, study period and, differences among studies.

Conclusion

The successful treatment rate among children was low compared to the national treatment success rate plan in the general population. Unsuccessful treatment rate was also high among children which are attributed to Lost to follow-up cases. Therefore, strengthening the DOTS program among children is desirable to decrease those Lost to follow-up cases and ultimately to improve the TB treatment outcomes among children in Ethiopia.

Implications for practice

There is a high treatment unsuccessful rate and poor treatment outcomes among children treated for tuberculosis compared with the national health sector transformation plan. The practice of using DOTs strategy to treat children should be strengthening and active case finding strategy should be advocated.

Implications for research

There are a number of observational retrospective studies on the treatment outcomes of childhood tuberculosis. However, there is urgent need for good-quality prospective cohort studies

that should also assess the possible risk factors of unsuccessful treatment outcomes (death, Lost to follow-up and failure) among children.

Declarations

Ethics approval and consent to participate: Not Applicable

Consent for publication: Not applicable

Availability of data and material: No additional data are required; all information is clearly presented in the main manuscript

Competing interests

We declare that we have no Competing Interest

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Authors' contributions

WB Conception of research protocol, study design, literature review, data collection, data extraction, data analysis and interpretation, and drafting manuscript. BT, Data collection and extraction, and reviewing manuscript. SE: Data analysis and reviewing manuscript. All authors have read and approved the manuscript.

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References

1. Hailu D, Abegaz WE, Belay M (2014) Childhood tuberculosis and its treatment outcomes in Addis Ababa: A 5-years retrospective study. *BMC pediatrics* 14:61.
2. Dodd PJ, Sismanidids C, Seddon JA (2016) Global burden of drug-resistant tuberculosis in children: A mathematical modelling study *Lancet Infect Dis* 16: 1193-1201.
3. Munoz SM, Yassin MA, Tumato M, Merid Y, Cuevas LE, et al. (2009) Treatment outcome in children with tuberculosis in southern Ethiopia. *Scandinavian journal of infectious diseases* 41: 450-455.
4. Tilahun G, Gebre-Selassie S (2016) Treatment outcomes of childhood tuberculosis in Addis Ababa: a five-year retrospective analysis. *BMC public health* 16: 612.
5. Ramos JE, Reyes F, Tesfamariam (2010) A Childhood and adult tuberculosis in a rural hospital In south east Ethiopia: A ten year retrospective study. *BMC public health* 10: 215.
6. Randall R, Sahil A (2016) As Ethiopia moves toward tuberculosis elimination, Success requires Higher investment. A report of the CSIS Global Health Policy center.
7. 1Tessema B, Muche A, Bekele A, Reissig D, Emmrich F, et al. (2009) Treatment outcome of tuberculosis patients at Gondar University Teaching Hospital, Northwest Ethiopia. A five--year retrospective study. *BMC public health* 9: 371.

8. Ejeta E, Chala M, Arega G, Ayalsew K, Tesfaye L, et al. (2015) Outcome of tuberculosis patients under directly observed short course treatment in western Ethiopia. *Journal of infection in developing countries* 9: 752-759.
9. Wong WCW, Cheung CSK, Hart GJ (2008) Development of a quality assessment tool for systematic reviews of observational studies (QATSO) of HIV prevalence in men having sex with men and associated risk behaviours. *Emerging Themes in Epidemiology* 5: 1742-7622.
10. Getah Ameni G, Medhin G, Biadgilign S (2013) Treatment outcome of tuberculosis patients under directly observed treatment in Addis Ababa, Ethiopia. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases* 17: 521-528.
11. Zenebe T, Tefera E (2016) Tuberculosis treatment outcome and associated factors among smear-positive pulmonary tuberculosis patients in Afar, Eastern Ethiopia: a retrospective study. *The Brazilian journal of infectious diseases : An official publication of the Brazilian Society of Infectious Diseases* 20: 635-636.
12. Kebede ZT, Taye WB, Matebe YH (2017) Childhood tuberculosis: management and treatment outcomes among children in Northwest Ethiopia: A cross - Sectional study. *Pan African Medical Journal* 27: 25.
13. Biruk M, Yimam B, Abrha H, Biruk S, Amdie FZ, et al. (2016) Treatment Outcomes of Tuberculosis and Associated Factors in an Ethiopian University Hospital. *Advances in Public Health* 1-9.
14. Tefera F, Dejene T, Tewelde T (2016) Treatment Outcomes of Tuberculosis Patients at Debre Berhan Hospital, Amhara Region, Northern Ethiopia. *Ethiopian journal of health sciences* 26: 65-72.
15. Mekonnen D, Derbie A, Mekonnen H, Zenebe Y (2016) Profile and treatment outcomes of patients with tuberculosis in Northeastern Ethiopia: a cross sectional study. *African health sciences* 16: 663-670.
16. Belayneh T, Kassu A, Tigabu D, Asmare G, Tilaye S, et al. (2016) Characteristics and Treatment Outcomes of "Transfer-Out" Pulmonary Tuberculosis Patients in Gondar, Ethiopia. *Tuberculosis research and treatment* 2016.
17. Endris M, Moges F, Belyhun Y, Woldehana E, Esmael A, et al. (2014) Treatment Outcome of Tuberculosis Patients at Enfraz Health Center, Northwest Ethiopia: A Five-Year Retrospective Study. *Tuberculosis research and treatment* 1-11.
18. Addis Z, Birhan W, Alemu A, Mulu A, Ayal G, et al. (2013) Treatment outcome of tuberculosis patients in Azezo health center, North West Ethiopia. *International Journal of Biomedical and Advance Research* 4: 167.
19. Sinshaw Y, Alemu S, Fekadu A, Gizachew M (2017) Successful TB treatment outcome and its associated factors among TB/HIV co-infected patients attending Gondar University Referral Hospital, Northwest Ethiopia: an institution based cross-sectional study. *BMC infectious diseases* 17: 132.
20. Zenebe Y, Adem Y, Mekonnen D, Derbie A, Bereded F, et al. (2016) Profile of tuberculosis and its response to anti-TB drugs among tuberculosis patients treated under the TB control programme at Felege-Hiwot Referral Hospital, Ethiopia. *BMC public health* 16:688.
21. Biadlegne F, Anagaw B, Debebe T, Anagaw B, Tesfaye W, et al. (2013) A retrospective study on the outcomes of tuberculosis treatment in Felege Hiwot Referral Hospital, Northwest Ethiopia. *International Journal of Medicine and Medical Sciences* 5: 85-91.
22. Tadesse S, Tadesse T (2014) Treatment success rate of tuberculosis patients in Dabat, northwest Ethiopia. *Health* 6: 306-310.