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Factors associated with zoonosis and reverse zoonosis of mycobacterium tuberculosis and mycobacterium bovis in Ethiopia: A systematic review and meta-analysis

Getahun Bahiru Desta
School of Public Health, Kalinga Institute of Industrial Technology (KIIT) Deemed to be University, Bhubaneswar, Odisha, India
Corresponding author email: gemb2372@gmail.com; 1781143@kiit.ac.in

Pratap Kumar Jena
School of Public Health, Kalinga Institute of Industrial Technology (KIIT) Deemed to be University, Bhubaneswar, Odisha, India

Hailemariam Mamo Hassen
School of Public Health, Kalinga Institute of Industrial Technology (KIIT) Deemed to be University, Bhubaneswar, Odisha, India

Manas Ranjan Behera
School of Public Health, Kalinga Institute of Industrial Technology (KIIT) Deemed to be University, Bhubaneswar, Odisha, India

***Abstract*---**Zoonotic TB (M.bovis) is transmitted from animals to people. Mycobacterium tuberculosis is responsible for the transmission of reverse zoonotic tuberculosis from humans to animals. Without sufficient proof, a few recommendations can be made regarding zoonotic and reverse zoonotic transmission. The researchers aimed to review and meta-analysis of risk variables for zoonotic and reverse transmission of bovine tuberculosis. Until May 2022, 13 published publications from Pub-Med, Scopus, Web of Science, and Google Scholar were identified for review using the PRISMA checklist. The findings revealed that increasing age, raw milk and meat consumption, lack of knowledge, human and animal contacts were strongly associated with zoonotic TB. A house without ventilation and presence of TB case in the household were all strongly linked to the risk of reverse zoonotic tuberculosis, but gender being male was not significantly associated with the reverse zoonosis of tuberculosis ($p > 0.05$). Addressing these risk factors would aid in

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preventing and controlling zoonotic and reverse zoonotic tuberculosis in Ethiopia.

***Keywords*---**Ethiopia, Reverse zoonosis TB, Risk-factors, Zoonosis TB.

Introduction

Tuberculosis (TB) is a contagious illness affecting humans and animals. Mycobacterium tuberculosis causes most human tuberculosis, while Mycobacterium bovis (M. bovis) causes most animal TB. M. bovis causes zoonotic tuberculosis and animal-to-human transmitted tuberculosis. Reverse zoonotic TB is spread from humans to animals by Mycobacterium tuberculosis. Both M. tuberculosis and M. bovis affect pulmonary and extra-pulmonary sites resulting in pulmonary tuberculosis (EPTB) and extra-pulmonary tuberculosis (PTB), which are difficult to distinguish from each other. In 2016, there were 147,000 newly recorded cases of zoonotic tuberculosis worldwide, with 12,500 people losing their lives to the disease(WHO, 2017). The level of zoonotic tuberculosis in the African region was the greatest, followed by the level in the South-East Asian region (WHO, 2017).

Tuberculosis found in cattle can be passed on to humans either through the consumption of raw or undercooked contaminated animal products, such as milk and meat, or through inhalation of the TB spores produced when cattle and humans come into close contact with one another. Mycobacterium tuberculosis thrives in locations where milk pasteurization is rare. About 10–15% of tuberculosis cases are attributed to M. bovis(Ashford, Whitney, Raghunathan, & Cosivi, 2001).

Reverse zoonosis, in which a disease spreads from humans to cattle, is a source of concern for both animal and human health because animal disease reservoirs could emerge (Messenger, Barnes, & Gray, 2014). Humans are assumed to be the main reservoir for M. tuberculosis. A diverse spectrum of hosts can become infected by tubercle bacilli, and M. tuberculosis has been found in animals, even though the human-to-human infection cycle rotates. In these animals, the Mycobacterium TB infection was almost certainly transmitted by humans. However, the infection can also occur in animals, which can subsequently cause infection in people (BhanuRekha, Gunaseelan, Pawar, Nassiri, & Bharathy, 2015; Une & Mori, 2007).

The acquisition, development, and epidemiological burden of tuberculosis are all linked to demographic characteristics; a lack of awareness and information regarding the illness's cause, transmission, and symptoms; a lack of health education; traditional habits of raw milk and meat consumption; close physical contact; socio-economic status; and traditional beliefs (Lönnroth & Raviglione, 2008). Although M. bovis is disseminated through raw milk (Kazwala et al., 1998), pulmonary tuberculosis cases have been reported, especially in rural regions where cattle are present (O'Reilly & Daborn, 1995).

Cattle can become infected with M. tuberculosis via TB patients' secretions. Cattle pathogens can be transmitted to cattle in several ways, including contaminated feed or aerosols (Cassidy, 2006; Costello, Doherty, Monaghan, Quigley, & O'Reilly, 1998), when the sufferer hacks up a cough or sneezes. Spitting sputum, which contains bacilli by a sick person, into drinking and feeding materials, the illness's causative agent could contaminate them, especially before treatment begins. Ingestion of contaminated water, feed, and fomites is another transmission route (Franck, Fonager, Ersbøll, & Böttiger, 2014; Gumi et al., 2012).

In Ethiopia, bovine tuberculosis (BTB) is the most common intensifying disease, and it significantly impacts livestock productivity. In the country's peri-urban areas, the disease's economic and zoonotic ramifications have been observed (Ayele, Neill, Zinsstag, Weiss, & Pavlik, 2004; Legesse et al., 2011). As a direct consequence, bovine TB is a significant issue in our nation, and it is particularly prevalent in cow populations. Its zoonotic ramifications have resulted in a significant increase in the risk of human public health threats (Legesse et al., 2011; Shitaye, Tsegaye, & Pavlik, 2007).

Ethiopia is not only one of the three African nations with the most tuberculosis cases but also one of the nations that are most afflicted by the disease (Organization, 2021). In Ethiopia, BTB is similarly widespread, ranging from 3.4% in smallholder Zebu herds to 50% in peri-urban (intensive) dairy herds; this disease is prevalent (Biratu et al., 2014; Bogale, Nigussie, & Seboksa, 2001; Firdessa et al., 2012). High livestock tuberculosis rates, close contact with humans in remote areas, community use of raw animal products, and the presence of HIV are all factors that may increase the risk of M. tuberculosis and other Mycobacterial infections being passed from animals to their owners (Shitaye et al., 2007).

Although the End TB Strategy aims to diagnose and treat every tuberculosis patient, recently, it was discovered that those at risk of contracting zoonotic TB had gone unnoticed. We need current and accurate scientific facts to alter how things are now perceived. As a result, a recent article focused on comprehensive surveys and high-quality data on zoonotic TB, "Roadmap for zoonotic tuberculosis" (Dean et al., 2018). Still, in low and middle-income countries, such as Ethiopia, there is currently no comprehensive evidence about the risk factors for spreading Mycobacterium tuberculosis and Mycobacterium bovis zoonotic infections.

As a result, our study would use a review and meta-analysis of previous observational studies to identify the associated risk factors and draw attention to the country's lack of studies on zoonotic and reverse zoonotic tuberculosis. Expertise in identifying and mitigating risk factors for tuberculosis transmission from animal to human and vice versa in a global setting will aid in developing a research programme to fill knowledge gaps on this essential but understudied disease.

Materials and Methods

Study Protocol

The protocol of this systematic review was developed following (**Figure 1)** the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines(Page et al., 2021).

Eligibility Criteria and Outcomes Definition

Ethiopian researchers investigated the influence of risk factors for zoonotic and reverse zoonotic transmission. Outcome of interest was Effect Size (ES) i.e. Odds ratio of different risk factors of zoonotic and reverse zoonotic transmissions in Ethiopia.

Data Source and Search Strategy

We examined five online databases for published articles to discover probable relevant studies on zoonotic and reverese-zoonotic tuberculosis in Ethiopia: Science Direct, Web of Science, Scopus, Pub Med, and Google Scholar were searched for relevant articles. A sensitive search strategy using key words such as 'bovine', 'human', 'cow', 'livestock', 'Tuberculosis', 'wasting sickness', 'Mycobacteriosis', 'zoonotic mycobacteria', 'M. tuberculosis', 'M. bovis', 'Risk Factors', 'Zoonosis', 'Reverse zoonosis', etc. were used to search the data base with the help of bulean operators. The search was limited to Ethiopia and fulltext artciles written in English langauge during last two decades (2000 AD onwards) to ensure study results are relevant in the current context. The strings were altered to phrase zoonotic and reverse zoonotic tuberculosis in Ethiopia as precisely as feasible. Additionaly, the bibliographic references of shortlisted articles were searched to identify additional relevant literatures if any.

Title and abstract screenings

The titles and abstracts were reviewed independently by two authors to ascertain the relevancy of this review. Only Ethiopia should be considered in terms of study sites and areas. The review removed abstracts, sessions, review papers, case and outbreak reports, studies published before 2000, poorly specified techniques, and ambiguous presentation of results.Authors examined cross-sectional and case-control studies that identified effect size of risk factors for the zoonotic and reverse zoonotic transmissions in the form of odds ratio. A complete selection process diagram was generated using PRISMA to show the number of studies selected and rejected, along with reasoning (Figure 1).

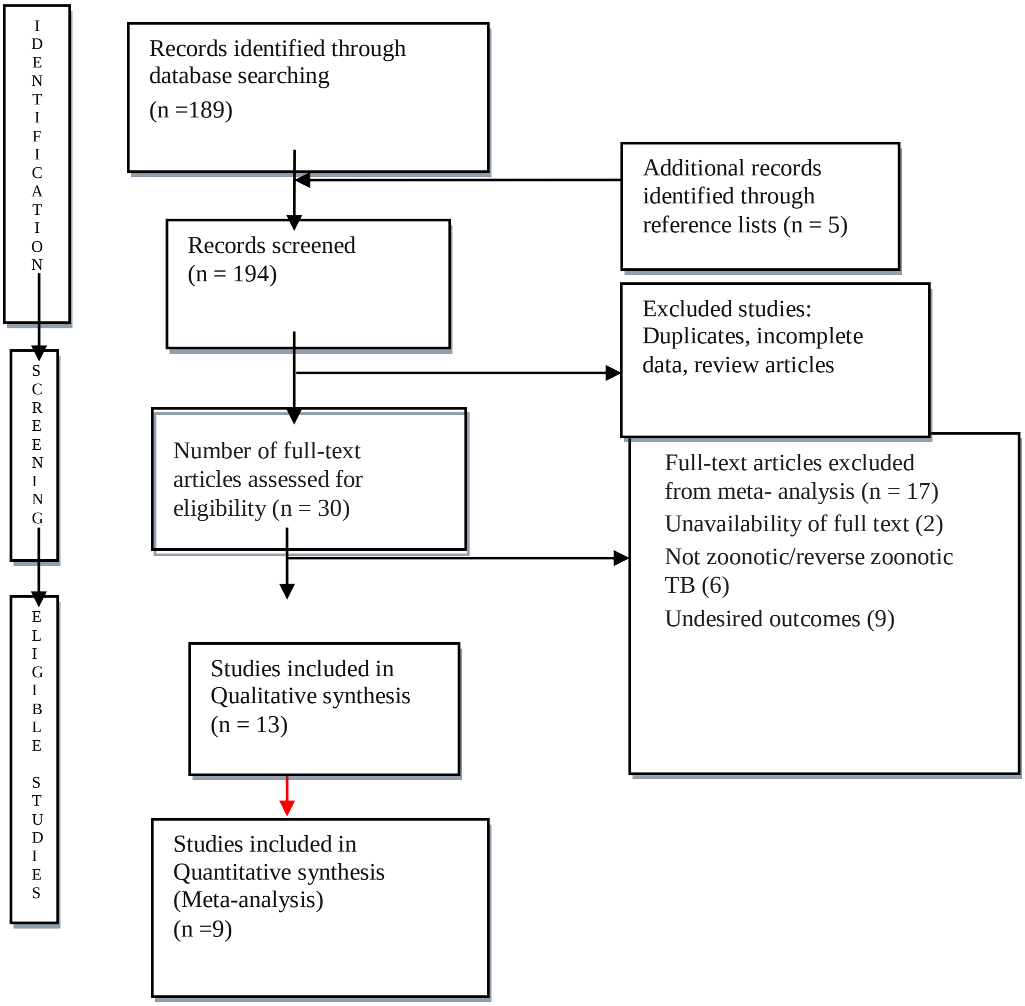


Figure 1: A PRISMA flow diagram of the studies chosen for a comprehensive review and meta-analysis of factors linked to zoonosis and reverse zoonosis of tuberculosis

Full-text review

When making our decision about whether or not to include the articles, we read through their complete contents. For all possibly relevant articles, full-text articles were obtained. The fulltext articles were subjected to independent review by two authors to rate the quality of publication, to review the methods and to extract the data as per protocol.

Data extraction

Data was collected using a table designed specifically for gathering research characteristics (authors' name, year of publication, study design, participants/samples, risk factors assessed, and how risk factors were measured). The odds ratios with 95% confidence interval values were gathered on characteristics that the study looked into as potential risk factors for M. bovis and M. tuberculosis zoonosis and reverse zoonosis. Among the predictors were socio-demographic, livestock-related characteristics, human knowledge of TB/BTB, human consumption habits, and human–livestock interface.

Data analysis
Descriptive analysis

In order to do a descriptive analysis, tables were made with odds ratios, 95 percent confidence intervals, and *p*-values. Initially the six groups of zoonotic risk factors and the reverse zoonotic seven groups of risk variables were identified. The zoonotic risk factors further grouped into two major subgroups i.e. contanct with animals and consumption of milk or meat of animals for meta-analysis. The 'contact with animals' as risk factos include Presence of cattle with TB in the household, Living with animals in same household, Having house without ventilation, Human and animal using common water sources, Sharing house with livestock, Physical contact with animal, Regular and direct contact with live animals, and Livestock shephering practice. For the purpose of meta-analysis we considered availability of atleast two studies for a given risk factors.

Mata-analysis

Strategy for data synthesis: This study estimated the pooled statistical parameter (Effect Size – Odds Ratio) in the meta-analysis using MetaXL (v.5.0) software. It is a free 'add-in' Microsoft Excel programme available at https://epigear.com website. Analyses were carried out to summarize the overall risk factors connected with zoonotic tuberculosis transmissions. In this meta-anlysis random effect model was preferred over heterogeneity model as all the studies were from same country and with expected limited heterogeneity among the studies. That is further confirmed from Cochrance Q and the I^2 value during the meta-analysis.

Result

Database search

All of the research that could be useful was conducted in English. In the beginning, we retrieved 194 papers from several *databases*, including Science Direct (15), Web of Science (9), Scopus (40), Pub-Med (25), and Google scholar (105). A total of 164 papers were eliminated from consideration once we viewed the titles and abstracts of the publications. Following this, a total of 30 full-text articles were analyzed. However, following a more in-depth review, 17 of these papers were omitted from the review; altogether, thirteen studies were included: four case-control and nine cross-sectional studies; as well as these, ten articles served as the foundation for the meta-analysis (Figure 1). In this study, the bulk of the papers concentrate on Mycobacterium bovis (n=4), Mycobacterium tuberculosis (n=2), or both Mycobacterium bovis and M. tuberculosis (n=7).

Characteristics of the report

The baseline features of the studies that were considered are shown in Table 1. The search was limited to articles written in the English language only. All of the chosen research was carried out in accordance with the methodologies of a cross-sectional and case-control study, and it was published between the years 2000 and 2021. Only animals were included in one study (Gobena Ameni et al., 2011). The research was carried out in a few selected regions of the country. The odds ratio and 95% confidence interval values on the habit of food consumption, knowledge regarding TB transmission, educational status, whether livestock was housed in the same shelter as their owners or housed in separate shelters, shared common water source, household TB status or the presence of TB cases in the family, number of cattle reactors to tuberculin skin test, regular and direct contact with live animals, practice spitting sputum, ventilation in the house, animal worker service year, types of animal breed, the origin of cattle owners, human urine being licked by cattle, and people urinate on animal feed was captured.

The Conceptual Definition and Qualitative Description of Risk Variables

In the descriptive table 2, which was in the form of a table, the conceptual definitions and qualitative explanations of 21 risk factors found to be linked to zoonosis and reverse zoonosis of tuberculosis were given.

Table 1: Overview of the selected studies

First Authors and Study year	Study location	Study design	Participants / Samples	Risk factors assessed	Risk factors measurement
Meseret *et al., 2016*	Central part Ethiopia	Cross-sectional	25 dairy farmers 558 head of cattle	Raw milk/ meat consumption, Age, TB knowledge, and Education status	Odds ratio/Chi-square
Fetene *et al., 2011*	North part of Ethiopia	Case-control	210 cattle owners 1220 cattle	Gender, age, contact, Origin, Milk consumption habit	Odds ratio
Ameni *et al., 2013*	The central part of Ethiopia	Case-control	287 households 2033 cattle	Sex, Age, Consumption of raw milk, Sharing house with animals, cattle breed, the residence of cattle owners, Animals grazing on the field, One or more of his/her animals have tested positive for tuberculosis, Thinks that he/she knows TB, Has TB positive family member, Know symptoms of TB, Cattle can be afflicted with tuberculosis, Believes	Odds ratio

				that tuberculosis can be passed from cattle to humans, Believes that animals can contract tuberculosis from humans.	
Kassa *et al., 2015*	Ethiopia's north-eastern and western regions	Case-control	150 households = 35 families with tuberculosis and 105 houses free of the disease.	Cattle TB status, House sharing, Urinating on hay/feed, Urine licking, House ventilation, Sputum spitting in the house, using the same source of water, Habit of taking unbilled milk	Odds ratio
Tschopp *et al., 2009*	Amhara, Oromia, and the SNNPR region of Ethiopia	Cross-sectional	780 cattle owners 2216 cattle	Cattle housing at night, Human TB cases, Raw milk consumption, Raw meat consumption, Number of cattle reactors, Shepherding	Odds ratio
Alelign *et al., 2019*	The northern part of Ethiopia	Cross-sectional	186 farmers 476 cattle	*Household TB status, Raw milk consumption*	Odds ratio
Ameni *et al., 2003a*	Central Ethiopia	Cross-sectional	94 household 763 cattle	Awareness about the transmission of tuberculosis, milk, and meat consumption habits, TB cases in the family history, livestock husbandry system	Chi-square
Berg *et al.,2015*	Northern, Southern, and Central parts of Ethiopia	Cross-sectional	953 PTB 1198 TBLN	Age, Sex, Intake of raw milk, Sharing a home with animals, having regular and direct interaction with animals	Odds ratio
Regassa *et al., 2008*	The central part of Ethiopia	Case-control	174 cattle owners 1041 cattle	Animal age, sex, body condition, breed, herd size	Odds ratio
Endalew *et al., 2017*	The central part of Ethiopia	Cross-sectional	62 dairy farm workers 720 cattle	Respondent's awareness of BTB, mode of transmission, history of TB cases in the family	Chi-square
Ameni *et al., 2007*	Central Ethiopia	Cross-sectional	378 household 524 cattle	Awareness of the transmission of bovine TB, consumption habit of meat and milk, history of TB cases in the family	Chi-square

Ameni *et al., 2011*	Central Ethiopia	Cross-sectional	52 cattle	Humans suffering from active TB, human and animal mouth-to-mouth' contact	Not measured
Kemal *et al., 2019*	Eastern Ethiopia	Cross-sectional	43 household 315 cattle	Respondent's awareness on BTB, mode of transmission, family history of tuberculosis, shared living quarters with livestock, meat and milk consumption habits	Not measured

Table 2: Conceptual definition of risk factors and qualitative explanation for zoonosis and/or reverse zoonosis of BTB/TB

Risk factors	Conceptual definition	Qualitative risk factors explanation for zoonosis	Qualitative risk factors explanation for reverse zoonosis
1. Gender	Social and cultural variations among human participants in studies that were related to their sexes	It is the social and cultural distinctions of the people who took part in the study, and these changes could be potential tuberculosis or BTB positive risk factors in people and livestock (Gobena Ameni et al., 2013; Broughan et al., 2016; Fetene, Kebede, & Alem, 2011).	It is the social and cultural distinctions of the people who took part in the study, and these changes could be potential tuberculosis or BTB positive risk factors in people and livestock (Gobena Ameni et al., 2013; Broughan et al., 2016; Fetene et al., 2011).
2. Age	Participants in the human trial, broken down by age group	The age groupings of the individuals that were studied could be a possible risk factor for tuberculosis or BTB positive in humans (Gobena Ameni et al., 2013; Bekele Meseret et al.,, 2016; Broughan et al., 2016; Fetene et al., 2011; Gompo et al., 2020).	The age groupings of the individuals that were studied could be a possible risk factor for tuberculosis or BTB positive in humans (Gobena Ameni et al., 2013; Bekele Meseret et al.,, 2016; Broughan et al., 2016; Fetene et al., 2011; Gompo et al., 2020).
3. Raw milk consumpti on	Consuming milk that has not been pasteurized or cooked to eliminate microorganisms that can cause illness.	Consumption of milk that has not been pasteurized and meat that has not been cooked thoroughly could contribute to the propagation of tuberculosis (Bekele Meseret et al.,, 2016; Deneke et al., 2022; Fetene et al., 2011; R Tschopp et al., 2010).	
4. Consumpti on of raw meat	Any sort of raw animal muscle that is prepared for use as a food product	Meat that has not been prepared or raw meat from cattle that have tuberculosis could be the source of the disease in humans (most commonly Extra-pulmonary TB)(Lombard et al., 2021; Mengistu, Enquselassi, Aseffa, & Beyen, 2015; Rea Tschopp, Schelling, Hattendorf, Aseffa, & Zinsstag, 2009).	
5. Sharing house with livestock	Farmers kept their animals in their homes with them.	It is possible that the spread of tuberculosis (TB) among humans and positive skin test reactions in cattle could be increased by housing animals alongside humans in enclosed living quarters (Berg et al., 2015; Devi et al., 2021; Mengistu et al., 2015; Rea Tschopp et al., 2009).	It is possible that the spread of tuberculosis (TB) among humans and positive skin test reactions in cattle could be increased by housing animals alongside humans in enclosed living quarters (Favor zoonosis and reverse zoonosis) (Berg et al., 2015; Devi et al., 2021; Mengistu et al., 2015; Rea Tschopp et al., 2009).

6. Humansman and animals used common water source	Drinking water was obtained from a shared source for the farmers and their livestock.	Humans can contract tuberculosis (TB) through indirect contact after being exposed to water that has been tainted by the urine of animals that are sick with TB (Mengistu et al., 2015).	
7. Presence of TB cases in the household	It was determined that a household was a TB-positive household if it contained at least one person who had tuberculosis.		People who had tuberculosis and owned cattle were more likely to share their houses with their animals and to have animals that tested positive for PPD (Gobena Ameni et al., 2013; Fetene et al., 2011; S. Ibrahim et al., 2012; Rea Tschopp et al., 2009).
8. Regular and direct contact with live animals	Most commonly surviving in close proximity to and sustained interaction with live animals	Longer exposure could arise from close contact between tuberculosis-infected animals and people, which would very certainly raise the likelihood of disease transmission between the two populations (Berg et al., 2015).	
9. Education status	The socio-economic element, which was connected to people's awareness of zoonotic and reverse zoonotic TB transmission.	One of the risk variables that influence the occurrence of TB sickness is education. Because of a lack of information, many are unaware of how tuberculosis is transmitted and how dangerous it is. This results in an increased risk of contracting the disease (Bekele Meseret et al.,, 2016; Rusnoto, Nasriyah, Meitasari, & nisa, 2020).	
10. Knowledge of TB modes of transmission	The human participant's understanding of the mechanics of tuberculosis transmission	One of the most important factors in keeping diseases like tuberculosis from spreading is raising awareness about the possibility of disease transfer from cattle to people. The greater the public's awareness of the condition, the greater the likelihood that disease transmission from people to cattle will be reduced (Bekele Meseret et al.,, 2016).	
11. Spiting in	People who have an		It is medical negligence, and it would also

the house	infection or a persistent ailment that affects the lungs or the airways may be more likely to cough up sputum, and if they do, they may spit inside the house.		contribute to the propagation of disease. Cattle could become infected with tuberculosis by inhaling cough and spitting droplets from farmers who had active cases of the disease (Mengistu et al., 2015).
12. Cattle licking human urine	Animal keepers who use urine as a treatment for sickness or who let their animals lick the urine		The tubercle bacilli pass from humans to animals through infected urine; contributing to the continued spread of the disease. It's possible that tuberculosis sufferers who own animals are a constant source of infection for those animals (Mengistu et al., 2015).
13. Human urination practice on cattle's' feed	urinating on cow feed or hay as a habit or practice		This could have been caused by infected people urinating on animal feed, which would then become contaminated with tubercle bacilli and be consumed by animals. This was one of the possible explanations for this contribution. Owners of infected cattle run the risk of being infected themselves and spreading the disease to their herds (Mengistu et al., 2015).
14. Having a house without ventilation	House devoid of any windows or other openings that would allow air circulation.		Inadequate house ventilation can lead to dilution or removal of infectious droplet nuclei insufficient, which can contribute to tuberculosis transmission between humans and animals living in the same house (Mengistu et al., 2015).
15. Perception about TB cannot be transmitte d from animals to human	Participants in the study frequently had either the correct or incorrect perception that the disease or bovine tuberculosis can be passed from cattle to humans.	Participants in the study were led to believe that there was a chance of stopping the transmission of disease from cattle to humans; however, there was no evidence to support this hypothesis (Gobena Ameni et al., 2013; Bihon, Zinabu, Muktar, & Assefa, 2021).	
16. Know	Participants in the	There is a possibility that owners of	

cattle can be infected with TB	study frequently were not aware that animals may get tuberculosis from humans.	livestock are familiar with the illness; as a result, they might have a better chance of stopping the disease from spreading from people to cattle if they do this (Gobena Ameni et al., 2013).	
17. Positives skin test reactor cattle	If the skin thickness is greater than 4mm at the bovine PPD injection site, the animals are considered to have BTB.		The skin test is extremely specific, which means that we can be confident that the vast majority of animals that tested positive for the disease using the skin test were situated in a region where the incidence of the disease is very high and may pose a danger to transmit it. Bovine tuberculosis can be contracted by those who own cattle, as well as those who come into touch with infected animals or the products of infected animals (District, 2003).
18. Residential area of cattle owners	The residential location of the participants in the study, which could be either rural or urban.	If people who live in the rural areas and their housing was in disrepair, they had limited access to medical facilities, they had a limited understanding of diseases, and they typically shared their homes with their cattle. All of these variables contribute to the spread of tuberculosis between cattle and the people who own them (Fetene et al., 2011).	
19. Livestock shepherding practice	Humans of all ages are responsible for caring for and guarding a herd of cattle.		In the setting of Ethiopia, Most herding is done by youngsters or by a team of children and adults, and the regular and prolonged exposure that results from this practice increases the likelihood of disease transmission between the two populations (Rea Tschopp et al., 2009).
20. Animals grazing on the field	It is a method of cattle management known as extended grazing, in which the owners give their animals access to unrestricted fields in which to graze.	Diseases that affect livestock, such as bovine tuberculosis, have a direct link with animal husbandry systems; the development of animal husbandry systems is increasing the prevalence of the disease, which poses a considerable public health risk for people who consume animal products (Rea Tschopp et al., 2009).	

21. Types of animal breeds owned by Farmers	The research animals were divided into two categories: native zebu breeds and mixed breeds (Holstein and zebu).	There is a possibility that the introduction of cross breeds of cattle, sometimes known as exotic breeds, along with an increase in the intensity of animal husbandry without an accompanying tuberculosis testing and prevention programme aided in the progression of the disease by contributing to its spread (Vordermeier et al., 2012).	

Analytical findings synthesis

Nine of the 13 studies that were suitable for inclusion in the meta-analysis were chosen (Alelign, Zewude, Petros, & Ameni, 2019; G. Ameni & Erkihun, 2007; Gobena Ameni et al., 2013; Bekele Meseret et al.,, 2016; Berg et al., 2015; District, 2003; Fetene et al., 2011; Mengistu et al., 2015; Rea Tschopp et al., 2009). Out of the nine articles, three were case-control studies (Gobena Ameni et al., 2013; Fetene et al., 2011; Mengistu et al., 2015), while the other six were cross-sectional study designs (Alelign et al., 2019; G. Ameni & Erkihun, 2007; Bekele Meseret et al.,, 2016; Berg et al., 2015; District, 2003; Rea Tschopp et al., 2009). During the process of statistical analysis, the odds ratio, as well as the confidence interval, were assessed and recorded. The list of predisposing factors related to zoonosis and reverse zoonosis of tuberculosis were gender, age, raw milk consumption, consumption of raw meat, sharing a house with livestock, human and animal use of common water sources, cases of tuberculosis in the household, regular and direct contact with live animals, knowledge of TB transmission modes, spitting in the house, cattle licking human urine, the practice of humans urinating on livestock feed, Having a house without ventilation, TB perception cannot be passed from animal to human, cattle can be infected with TB, cattle that pass the skin test, and cattle owners' neighborhoods Livestock shepherding practices, animals grazing on fields, and types of animal breeds owned by farmers.

We evaluated 21 possible risk factors for zoonotic tuberculosis as well as reverse zoonotic transmission of the disease (Table 2). In the process of doing a meta-analysis, variables that were thought to be redundant and had a frequency of more than 10 percent were consolidated into a single variable. For the purpose of descriptive analysis, the values for the odds ratio and the confidence interval for 95% of the data that were gathered were summarized. The data was then grouped into six groups for zoonotic risk factors and seven groups for reverse zoonotic risk factors.

Increasing age (odds ratio 4.55; 95% CI: 1.80-7.34) (OR 4.55; 95% CI: 1.80-7.34)(Bekele Meseret et al.,, 2016), consuming raw milk and meat (OR 3.47; 95% CI: 1.51-7.94)(Mengistu et al., 2015), having no knowledge (OR 3.11; 95% CI: 1.92-5.04), human and animal contact (OR 3.78; 95% CI: 1.48-6.67, OR 3.00; 95% CI:1.90-4.50, OR 4.17; 95% CI: 2.43-6.77)(Gobena Ameni et al., 2013; Berg et al., 2015) were strongly associated with zoonotic tuberculosis (Figure 2).

Raw animal product consumption-based grouping showed that 1.75 was the overall pooled effect size for milk or meat consumption (CI: 1.21-2.54) (figure 3A), 1.73 milk consumption (CI: 1.16-2.60) (Figure 3B), and 1.88 for meat consumption (CI: 0.61-5.79) (Figure 3C). Direct or indirect human and animal contact-based grouped analysis showed that the overall pooled effect size was 2.18(CI: 1.66-2.85) (Figure 3D). No significant association between zoonotic tuberculosis and raw milk consumption, but found a significant association between zoonotic tuberculosis and meat consumption. The meta-analysis also indicated that the association is not statistically significant between zoonotic tuberculosis vs. direct or indirect contact ($P > 0.05$) (Figure 3D).

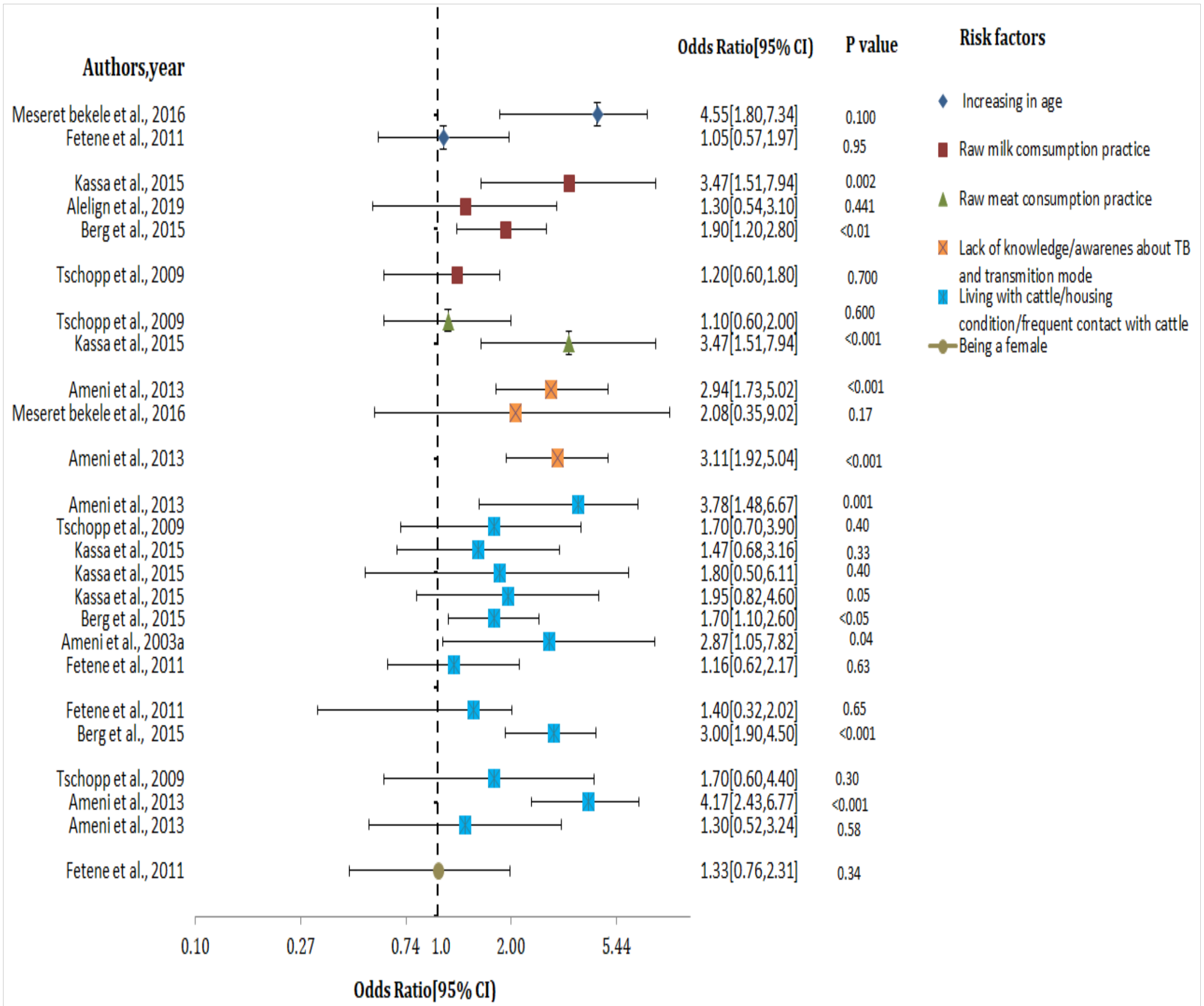
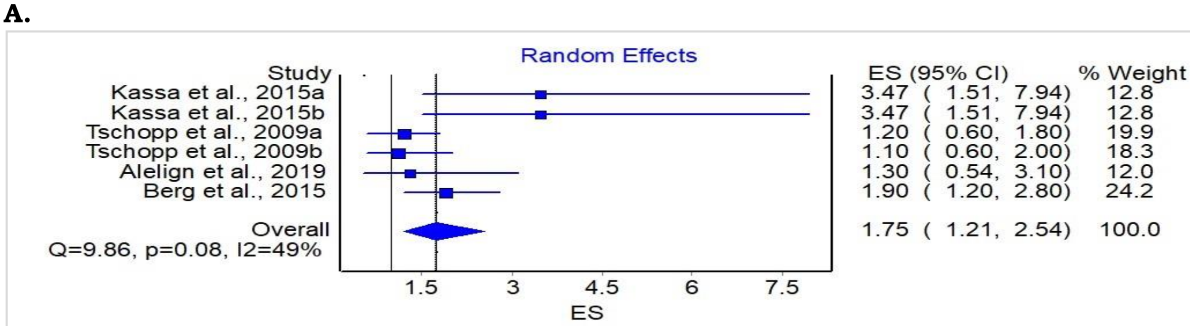


Figure 1: Forest plot for risk factors associated with zoonotic transmission of tuberculosis

A.



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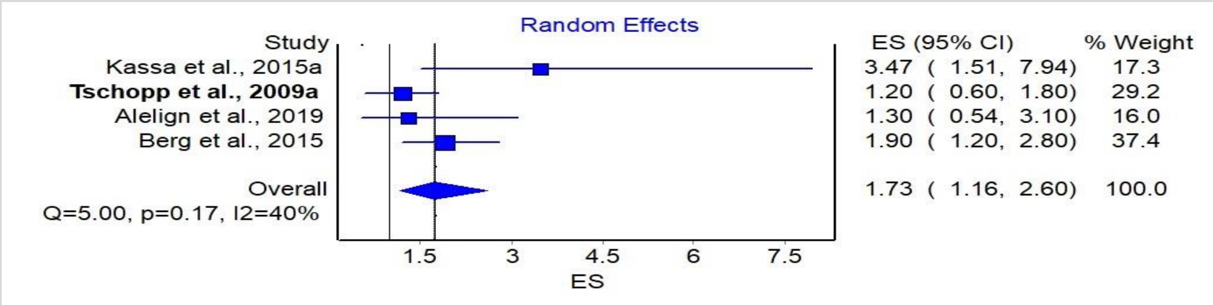
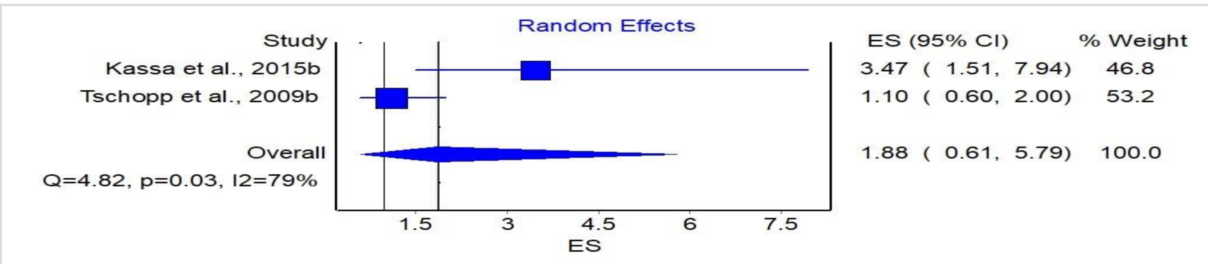


C.



D.

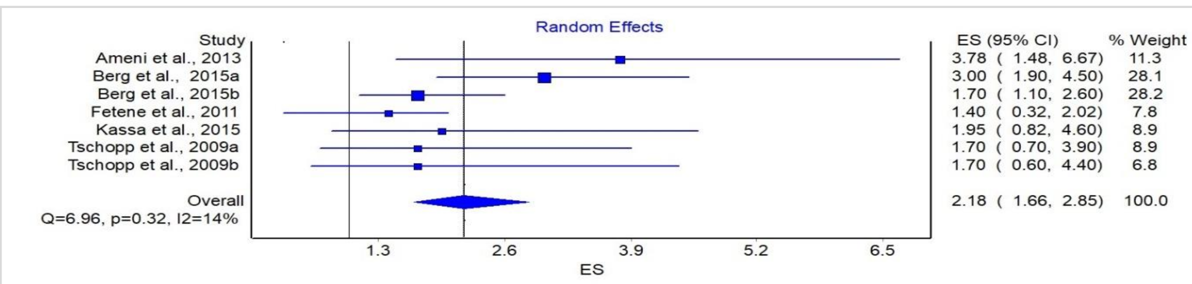


Figure 3: Forest plot of raw milk or meat consumption, raw milk consumption, raw meat consumption and direct or indirect contact associated with zoonotic tuberculosis

Note: **A.** *Milk or meat consumption vs. zoonotic tuberculosis* **B.** *Milk consumption vs. zoonotic tuberculosis* **C.** *Meat consumption vs. zoonotic tuberculosis* **D.** *Direct or indirect contact vs. zoonotic tuberculosis*

A house without ventilation (OR 5.50; 95% CI: 1.60-11.90)(Bekele Meseret et al., 2016), presence of TB case in the household (OR 4.52; 95% CI: 3.24-6.32 and OR 7.14; 95% CI: 3.30-9.44)(G. Ameni & Erkihun, 2007; Fetene et al., 2011), were all strongly associated with reverse zoonotic transmissions of Mycobacterium tuberculosis, but gender being male was not significantly associated with the reverse zoonosis of tuberculosis (p >0.05) as shown in Figure 4.

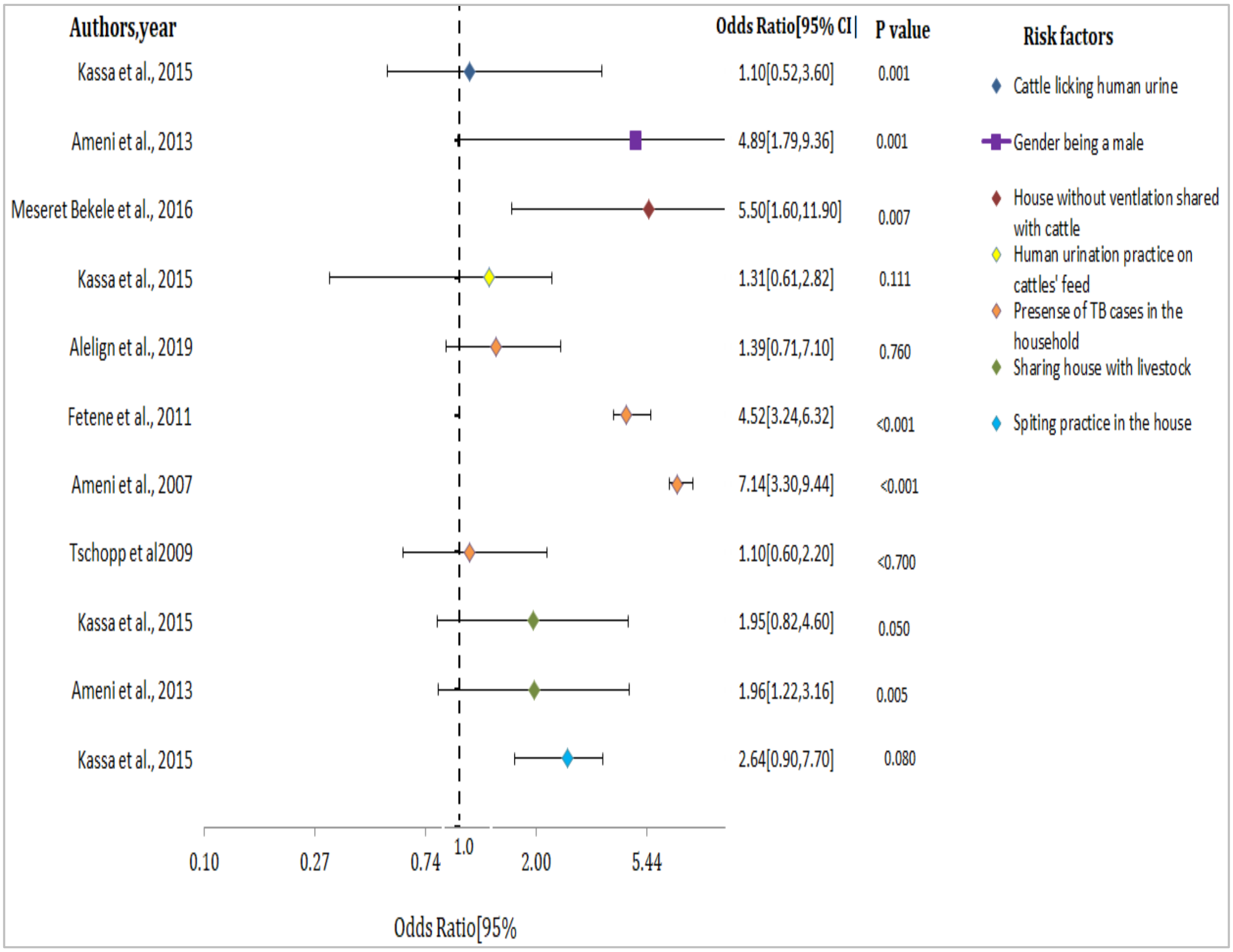


Figure 4: The forest plot for risk variables related to reverse zoonotic transmission of tuberculosis

Discussions

Over the next several decades, animal husbandry practices, growing human and animal populations, increased human and animal regular and direct contact, global travel and commerce, and increased interest in animal product consumption are expected to improve human and animal ties (World Bank, 2009). As human-animal interaction becomes more intense, the risk of illness zoonosis and reverse zoonosis increases (DeHart, 2003; Wilson et al., 2011). This study looks at several possible risk factors for the spread of zoonotic and reverse zoonotic tuberculosis from animals to humans and back again.

This is the first review and meta-analysis that we are aware of that focus on identifying risk factors for zoonotic and reverse zoonotic tuberculosis in people and animals. Previously, only zoonotic or reverse zoonotic tuberculosis had been studied in people and animals. The human-to-animal transfer of zoonotic diseases and vice versa served as the basis for the selection of the criteria that are detailed above and presented in the tables. Given the increased emphasis on associated risk factors and their odds ratio and 95 percent confidence interval, articles indexed and published in the last twenty years were considered; the study's type of study design was considered to assess not only a variety of risk factors but also to predict humans and animals at risk of zoonotic and reverse zoonotic TB infection and with which the animal and human involved make direct or indirect contact.

This review enabled us to determine the factors related to zoonosis and reverse zoonosis of Mycobacterium tuberculosis and Mycobacterium bovis were: Age, raw milk consumption, consumption of raw meat, sharing a house with livestock, and Humans and animals' use of common water sources. Regular and direct contact with live animals Education level, knowledge of TB transmission modes, and perception cannot be passed from animal to human. cattle can be infected with TB. Cattle that pass the skin test, Cattle owners' residence area, Livestock shepherding practice Animals grazing on fields, and types of animal breeds owned by farmers were captured as zoonotic risk factors, while gender, sharing a house with livestock, presence of TB cases in the household, house-spitting, human urine-licked cattle, urinating on livestock feed, and having a house without ventilation were identified as risk factors for reverse zoonotic infection of tuberculosis.

In a number of studies, the relationship between animal-related risk factors and human tuberculosis infection or disease (zoonosis) as well as risk factors linked to human and animal tuberculosis infection or disease (reverse zoonosis) has been studied. In Ethiopia, two case-control and two cross-sectional investigations indicated a strong link between BTB exposure and TB disease in humans and TB exposure and TB infections or disease in livestock (G. Ameni & Erkihun, 2007; Gobena Ameni et al., 2013; Bekele Meseret et al.,, 2016; Berg et al., 2015; Fetene et al., 2011). The greater the reported odds ratio for zoonosis and reverse zoonosis (OR 4.55) due to advanced age and the odds ratio (OR 7.14) for the presence of TB cases in the home, respectively.

The consumption of raw milk and meat, as well as regular and direct contact, were found to be substantially linked to risk factors, 3.47; 95 % CI: 1.51–7.94; and 3.00; 95 % CI: 1.90–4.50, respectively, are the odds ratios for this study. No statistical significance association were found in the association between raw milk consumption vs. zoonotic tuberculosis and direct or indirect contact between human and animal vs. zoonotic tuberculosis according to the overall pooled effect size. However, several studies have found that long-standing dangerous feeding practices such as drinking raw milk, as well as widespread close animal-human contact (Gobena Ameni et al., 2011; Etter et al., 2006; Mengistu et al., 2015; Rea et al., 2013; Shitaye et al., 2007), have not been avoided in Ethiopia. In Ethiopia's rural communities, these variables are seen as key risk factors for the transmission of zoonotic tuberculosis and reverse zoonotic tuberculosis between humans and cattle (Berg et al., 2015).

The study participants' perceptions concerning the possibility of tuberculosis spreading from animals to humans were found to be strongly related risk variables, with odds ratios that read as follows: (OR 3.11; 95 % CI: 1.92-5.04). This could be because of a lack of awareness of the route of tuberculosis transmission and the fact that cattle might be infected, and families with livestock and other animals are less protected (Biffa et al., 2010; Etter et al., 2006; Kassa et al., 2012; Rea et al., 2013).

House sharing between humans and animals has been recognized as a higher risk factor for zoonotic TB, with a reported odds ratio of (OR 4.17; 95 % CI: 2.43-6.77). This degree of connection may explain why cattle harboring the Mycobacterium tuberculosis complex could cause human infection by producing droplet nuclei when coughing (Salisu Ibrahim et al., 2010). In this case, cattle owners who were TB positive were more likely to live with their animals(Mengistu et al., 2015).

One of the factors substantially related to zoonotic TB was the presence of tuberculosis-infected livestock in the household. Studies in Ethiopia have shown that there are a lot of cattle there, that people and cattle live close to each other, and that M. tuberculosis has been found in both livestock (Gobena Ameni et al., 2011, 2013; Berg et al., 2009) and milk samples

(Srivastava et al., 2008). This suggests that cattle may be directly involved in the spread of tuberculosis (Berg et al., 2015).

Other things that have been found to be risk factors for zoonotic tuberculosis include age, using the same water source like animals, having a high level of education, having cattle that react positively to skin tests, living in the same area as cattle owners, herding livestock, letting animals graze in fields, and the types of animal breeds that farmers own. However, these things are not strongly linked to risk, with odds ratio values of less than three.

The majority of farmers in the region do not have adequate room or amenities, so they are forced to maintain intimate touch with their animals. This is especially true at night when they bring their animals inside their homes. Diseases can be passed from humans to other animals. Reverse zoonosis caused by Mycobacterium TB has been linked to the male gender, with an odds ratio of (OR 4.89; 95% CI: 1.79–9.36). This involvement could be attributed to infected males urinating on livestock feed, which is then ingested by cattle (Lombard et al., 2021). Furthermore, tobacco chewing and injecting into cattle's mouths is a uniquely Ethiopian cultural habit, performed almost exclusively by male Ethiopian farmers. This could help spread tuberculosis directly from people to livestock (Gobena Ameni et al., 2011).

In the current review studies, the existence of a human tuberculosis case in the family was determined to be one of the factors strongly linked to Mycobacterium tuberculosis reverse zoonosis (OR 7.14; 95% CI: 3.30–9.44). There have also been reports of cattle infected with Mycobacterium tuberculosis (Alexander et al., 2002; Gobena Ameni et al., 2011; Michalak et al., 1998; Ocepek, Pate, Žolnir-Dovč, & Poljak, 2005; Pavlik et al., 2003; Schürch & van Soolingen, 2012; Sternberg, Bernodt, Holmström, & Röken, 2002; Une & Mori, 2007), and cattle are exposed by inhaling coughed aerosols from farmers with symptomatic pulmonary TB and eating contaminated pasture (Michalak et al., 1998; Pavlik et al., 2003).

However, other discovered risk factors for reverse zoonotic tuberculosis, such as spitting in the house, cattle licking human urine, and human urination practice on cattle feed, were not strongly associated with potential risks for the condition.

The study's strengths and limitations

The fact that it was the first review and meta-analysis of zoonotic and reverse zoonotic tuberculosis risk factors in Ethiopia was one of the review's strengths. Furthermore, for selected reporting items for review and Meta-analysis, the review followed the PRISMA declaration approach. This review, on the other hand, has some limitations. Some of the studies considered did not give an adjusted risk ratio. As a result, these studies were analyzed using the crude odds ratio. The fact that we only looked for English-language publications was another limitation. This meta-analysis was not filed with PROSPERO, which may have resulted in bias. Importantly, this meta-analysis was also carried out by review requirements. There is a potential for geographical bias because the studies were conducted in different parts of Ethiopia.

Conclusions and Recommendations

Despite its importance, zoonotic and reverse zoonotic tuberculosis have gotten little attention, particularly in Ethiopia. The systematic review reveals that lack of knowledge of TB symptoms can result in zoonotic TB transmission from animals to humans. The existence of TB-infected livestock in the household, regular and direct contact with live animals, gender being female, house ventilation, and the presence of human TB cases in the household were all strongly associated with the risk of zoonotic and reverse zoonotic transmissions of tuberculosis. Across the country, more well-designed observational analytical studies are critically needed. The findings of the study can be utilized to assist in the development and implementation of initiatives across the country aimed at prevention and control. Tuberculosis is a neglected tropical disease that can spread from animals to humans and back again. It needs to be looked at right away.

Conflicts of interest
The authors report no conflicts of interest with this work.

Author's Contribution: Getahun Bahiru designed the study, searched the literature evaluated the quality, extracted data, did the statistical analysis and wrote the the manuscript. Hailemariam Mamo contributed to the statistical analysis and edited the manuscript. Pratab Kumar Jena contributed to the statistical analysis, evaluated the quality,verified and edited the manuscript. Manas Rajan Behera verified the manuscript.

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