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RISK FACTORS FOR LATENT TUBERCULOSIS INFECTION (LTBI) AMONG HOUSEHOLD CONTACTS OF TB PATIENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Latent Tuberculosis Infection (LTBI) is a condition in which an individual carries the TB bacteria without showing symptoms of active disease. An estimated 2.3 billion people globally are infected with LTBI, with household contacts of TB patients identified as a high-risk group. This systematic review aims to identify risk factors for LTBI among household contacts of TB patients. We conducted a literature search using Science Direct, PubMed, and Google Scholar, covering the period from 2019 to 2024. Inclusion criteria included studies on LTBI risk factors among household contacts of TB patients, written in English or Indonesian, research articles, and participants who lived with an active TB patient for at least one night and/or had frequent interactions with the patient within three months prior to TB treatment, Interferon-Gamma Release Assays (IGRA) or Tuberculin Skin Test (TST) tests were required. We evaluated article quality using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist. Nine articles were included. LTBI risk factors among household contacts of TB patients include increasing age, male, occupation type (farmers or laborers or fishermen), duration of employment for more than 10 years, duration of working hours for more than 8 hours per day, contact with TB patients, sharing a bedroom with TB patients, bedroom density, overweight, and owning pets. Government, healthcare workers, and the society particularly household contacts of TB patients, must understand these LTBI risks to prevent further transmission and support the 2030 TB elimination program.

Keywords: latent tuberculosis infection, household contacts, index TB case, TB patients

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* bacteria, primarily transmitted through airborne droplets from coughing. Although TB can affect nearly all organs except hair and nails, it predominantly targets the lungs.[1] This disease can affect all organs of the human body except hair and nails, but generally attacks the lungs. TB is treatable and curable, with treatment taking at least 6 months. By 2022, TB was the second leading cause of death in the world after COVID-19, which doubled the risk of death in people living with HIV/AIDS.[2]

TB cases worldwide rose from 2017 to 2019, yet new case reports declined by 18% during the COVID-19 pandemic (2019-2022), falling from 7.1 million to 5.8 million, even as an estimated 10.6 million people had TB in 2022. Additionally, TB caused 1.3 million deaths in 2022, with a treatment success rate of approximately 70%.[2] These figures suggest a significant gap between reported cases and actual infections. Research by Houben estimates that a quarter of the global population has been infected with TB, with 5-10% at risk of progressing to active TB within two years. Individuals infected with TB who do not develop active symptoms are considered to have Latent Tuberculosis Infection (LTBI), a condition in which the immune system contains the bacteria without causing symptoms.[3]

Despite estimates suggesting that 2.3 billion people globally have LTBI, certain groups are at elevated risk. High-risk groups include individuals living with HIV, children under five who are household contacts of TB patients, and other close contacts frequently exposed to TB patients.[4] Close contacts or household contacts with TB patients are also at high-risk of developing active TB.[5] World Health Organization (WHO) defines that close contacts or household contacts as people who live in the same house as active TB patients for one night or more, as well as people who frequently interact with TB patients even outside the home within the 3 months before TB patients undergo the treatment.[6]

The prevalence of LTBI among household contacts of TB patients is notably high. A study by Fox[7] reported that the prevalence of LTBI among household contacts is 28.1%, meaning that for every 10 individuals living in the same house with TB patient, approximately 2 to 3 are likely to develop LTBI. Meanwhile, research from India, which has the highest TB burden globally, indicated that the prevalence of LTBI among household contacts aged over 45 years ranges from 47% to 65%. Furthermore, if household contacts have comorbidities such as Diabetes Mellitus and malnutrition, the prevalence increases significantly, reaching up to 81%.[8]

Household contacts of TB patients should undergo testing with the Tuberculin Skin Test (TST) or Interferon Gamma-Release Assay (IGRA) to confirm LTBI status, facilitating management in line with WHO recommendations.[9] LTBI management can be done by providing Tuberculosis Preventive Therapy (TPT).[10] Several TPT options recommended by WHO need to be

adjusted to the patient's condition, including daily isoniazid monotherapy with treatment duration options ranging from 6, 9, and 36 months, daily rifampicin and isoniazid for 3-4 months, daily rifampicin monotherapy for 3-4 months, and daily rifapentine and isoniazid for 3 months.[11]

Basically, the 2050 TB eradication strategy will not be achieved if one of the programs, namely LTBI detection and treatment, is not implemented according to recommendations.[10] Globally, LTBI detection still does not have single data, but is incorporated into data on TB diagnosis, treatment, and access to prevention, which amounted to 5.8 billion. This number is still far from the target of 13 billion people in 2022.[2] Coverage of TPT in LTBI patients during 2018-2022 reached 15.5 million of the targets of 30 million people by 2050. Meanwhile, TPT administration in people living with HIV exceeded the target of 11.3 million against a target of 6 million. In children <5 years of age in close contact with TB patients, 2.2 million have been reached against a target of 4 million by 2050. However, the provision of TPT for close contacts aged ≥5 years is still slow, with only 2 million of the targets of 20 million by 2050.[2]

Seeing that single data on LTBI detection does not yet exist and the provision of TPT is still relatively low, there is a significant gap in services aimed at strengthening and expanding community outreach for detection, treatment, and TPT services.[9] While some research has explored the cost implications of LTBI interventions, such as the study by Satyanarayana[12] which showed that the cost of systematic screening of household contacts is lower than the provision of TPT (USD 288 million versus USD 392 million), few studies have specifically focused on analyzing the risk factors for LTBI among household contacts. This gap highlights the need for targeted research to identify individuals at the highest risk of LTBI, which could serve as the basis for developing timely and cost-effective prevention programs.[5] By systematically reviewing studies from 2019–2024, this research aims to address this gap by identifying key risk factors for LTBI among household contacts. This contribution is expected to support the development of evidence-based screening strategies and improve global TPT coverage.

Methods

This study utilized a systematic review design, employing a descriptive narrative synthesis for analysis. The population for this study includes all journals or articles related to risk factors for LTBI among household contacts of TB patients found in the databases of Science Direct, PubMed, and Google Scholar. Articles were selected using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart, based on predefined inclusion and exclusion criteria.

Inclusion criteria for this review were: articles published between 2019 and 2024, written in English or Indonesian, that investigated LTBI risk factors among household contacts of TB patients. Eligible studies included participants who lived with an active TB patient for at least one

night or who frequently interacted with the patient within three months prior to treatment initiation, with testing conducted via either the TST or IGRA. The exclusion criteria for this review were: journals or articles that use only univariate analysis; research with a retrospective cohort study or experimental study design; samples consisting of children aged ≤5 years; pregnant and breastfeeding women; individuals with a history of TB; and people living with HIV/AIDS.

Literature search process used the PRISMA guidelines consist of identification, screening, eligibility, and inclusion. The keywords used are as follows: ("risk factor" OR "determinant" OR *"Faktor risiko")* AND (*"kontak erat"* OR "close contact" OR "Household contact" OR *"Kontak serumah")* AND (*"Pasien TB"* OR "TB Patient") AND *("Infeksi Laten Tuberkulosis"* OR *"ILTB"* OR *"*Latent Tuberculosis Infection" OR *"*LTBI*"* OR *"TB Laten"* OR *"*Latent TB"). The initial search involves entering keywords into journal or article database search engines such as Science Direct, PubMed, and Google Scholar. Subsequently, journals or articles that appear are selected using automatic filters by applying criteria, such as publication years (2019-2024), languages (Indonesian and English), and research article type only.

The initial screening was conducted by the primary researcher (Author), who skimmed titles and abstracts, followed by a review of the methods sections to assess whether studies met the inclusion and exclusion criteria. Selected articles were then imported into Mendeley for further analysis. The following stage involves reading the journal or article thoroughly. Data from each article were organized into a tabular matrix that included author and publication year, study design, sample characteristics, sample size, LTBI detection tools, LTBI prevalence, results, and Literature Quality (LQ).

The quality of each study was then evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[13] To minimize bias, the STROBE checklist ensures a systematic evaluation of eight points including the sample size, study design, response rate, outcome measurement, statistical analysis, confounding variables, ethics approval, and study limitations. There are three classifications of literature quality: poor (0-3), moderate (4-6), and good (≥7).[14] Studies included in this research were those scoring 7 or higher. However, if a study scored below 7 but was deemed essential for context, it was still included with the addition of other supporting references to strengthen the findings. The final stage is inclusion, with the narrative synthesis method used for qualitative analysis, which is then further examined.[4]

Results

A total of 2,866 articles were retrieved in Science Direct, PubMed, and Google Scholar between 2019 and 2024. Of these, 1,937 articles were automatically excluded based on initial criteria, leaving 929 articles for further review. After screening titles and abstracts, 27 articles were selected, with 902 excluded. Further full-text review of these articles led to the inclusion of 14

articles based on the inclusion and exclusion criteria. However, upon thorough reading, five articles were excluded due to mismatched sample definitions (n=4) and univariate analysis (n=1). Ultimately, nine articles were included in this study following the literature search process. Figure 1 illustrates the literature search process based on PRISMA.

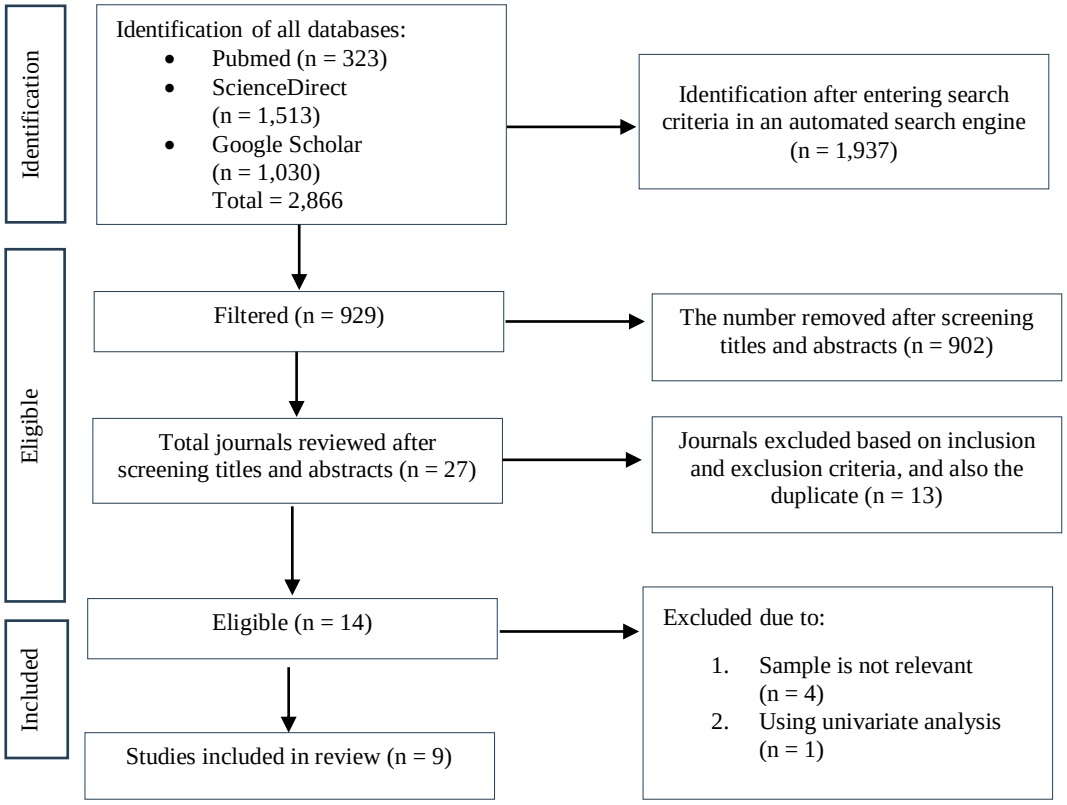

Figure 1. Literature Search Process Using PRISMA

Table 1 provides a tabular matrix of the findings from the reviewed articles. This study includes articles from various countries such as Indonesia, India, Burkina Faso, Panama, Thailand, Kenya, and Peru. Seven of these articles employed a cross-sectional study design, one used a prospective cohort design, and one study did not specify its design. The sample collected from different groups with sizes ranged from 61 to 2,621. Seven studies focused on household contacts of TB patients, while two others focused on healthcare workers, and one study discussed a mixed group of household contacts, healthcare workers, and slaughterhouse workers.

The sample criteria consisted of individuals living with TB patients (n=6), all articles have samples aged >15 years, those exposed to TB patients for a minimum of 3 months (n=4), individuals who shared meals with TB patients (n=1), and those who did not show clinical TB symptoms or have a history of TB illness (n=3). The LTBI tests used in these articles varied. Four articles used the Tuberculin Skin Test (TST), three used blood tests such as QuantiFERON-TB or

IGRA, and two articles used both TST and IGRA. The prevalence of LTBI incidence also showed varying results, ranging from 11.5% to 67.33%.

The studies obtained indicate ten risk factors for the occurrence of LTBI among household contacts of TB patients, including age >18 years (n=5), male (n=2), occupation type (laborers/ farmers/fishermen) (n=1), duration of employment for >10 years (n=1), duration of working hours for ≥8 hours/day (n=1), contact with TB patients (n=1), sharing a bedroom with TB patients (n=1), bedroom density (n=1), overweight (n=1), and having pets (n=1). The Literature Quality (LQ) assessment results show that the majority (n=7) fall into the good category (≥7), while the remaining (n=2) fall into the moderate category (4-6).

The table 1 summarizes findings from various studies on the risk factors associated with LTBI among different populations. The study conducted by Sangma[15] identified that women diagnosed with tuberculosis (TB) are more likely to expose their household members to LTBI. Odera[16] demonstrated that individuals aged 30-39 and 40-49 exhibit a significantly higher risk of developing LTBI compared to those aged 18-29. Krishnamoorthy[17] found that individuals over 18 years old who share sleeping arrangements with TB patients are more susceptible to LTBI.

Study from Klayut[18] found healthcare workers above the age of 40 and with over 10 years of professional experience were statistically more likely to contract LTBI, suggesting a positive correlation between work duration and risk infection. Karbito[19] identified that the primary determinants for LTBI incidence include occupation type (e.g., labourers, farmers, fishermen), duration of contact (≥5 hours/day) with TB patients, and bedroom density.

The cohort study by Nababan[20] concluded that advancing age and male are significant risk factors for LTBI development. Djibougou[21] similarly found that male gender and the presence of pets in the household were associated with a higher likelihood of LTBI. Cubilla-Batista[22] reported that individuals over 50 years of age and those classified as overweight are at increased risk for LTBI. Wardani[23] determined that healthcare workers with a history of contact with TB patients, particularly those who work ≥8 hours per day, are at elevated risk of developing LTBI.

Table 1. Matrix of Article Findings

Author & Year	Study Design	Sample Criteria	Total Sample	LTBI Detection Tool	LTBI Prevalence	Result	LQ
Sangma (2023)[15]	Cross-sectional	Individuals living with TB index cases and sharing food from the same kitchen for at least three months prior to the diagnosis of TB.	330	TST	26.4%	Women with TB are more likely to expose their household members to latent TB (Adjusted odds ratio 2.32; 95% confidence interval 1.07-5.05; p=0.03).	6
Odera (2020)[16]	Cross-sectional	Adults who share food and a room with TB patients and live together.	174	IGRA	55.7%	Individuals aged 30-39 years [OR = 1.82 (0.87 - 3.79), p = 0.110] and 40-49 years [OR = 1.60 (0.63 - 4.07), p = 0.317] have a higher risk of developing LTBI compared to those aged 18-29 years.	7
Krishnamo-orthy (2021)[17]	Cross-sectional	Adults and children who are not sick with TB but have been exposed to TB patients for at least three months.	597	TST	52.6%	Being over 18 years old (19–-64 years: Adj. IRR 1.3, 95% CI: 1.1–-1.5, p value 0.02 & ≥65 years: Adj. IRR 1.4, 95% CI: 1.1–-1.9, p value 0.02) and sleeping with TB patients (Adj. IRR 1.2, 95% CI: 1.1–1.3, p value: 0.04) contributes to the incidence of LTBI.	8
Klayut (2024)[18]	Cross-sectional	Healthcare workers who have been employed in the hospital for at least six months.	269	IGRA	40.89%	Healthcare workers over the age of 40 and with more than 10 years of work experience statistically have a positive association with the incidence of LTBI (OR = 3.21, 95% CI: 1.84-5.64, p-value < 0.05, and OR = 3.19, 95% CI: 1.66-6.37, p-value < 0.05.	7
Karbito (2022)[19]	Cross-sectional	Family members in contact with active TB patients, aged 15-70 years, and without clinical symptoms of TB.	138	TST	63.8%	The main factors for the incidence of LTBI are occupation type (laborers/ farmers/fishermen) (AOR:7.04; 95% CI:1.70–29.02, p=0,024), duration of contact for ≥5 hours/day with TB patients (AOR: 4.70; 95% CI:1.33–16.66), p=0,016, and bedroom density (AOR: 5,33; 95% CI:2.44–12.71, p=0,000).	7
Nababan (2024)[20]	Cohort Prospec-tive	Individuals living in the same household as active TB patients for one night or more, or those who interact with TB patients during the day for three months prior to the diagnosis of TB.	2,621	TST and IGRA	45.7%	Increasing age (aOR 1.01, 95%CI 1.01–1.02 p-value: 0,000) and female gender are low odds of LTBI (aOR 0.77, 95% CI 0.61–0.97, p-value: 0,0248).	7
Djibougou (2022)[21]	Cross-sectional	Household contacts with TB patients, health-care workers, and workers in slaughterhouses.	101	IGRA and TST	IGRA = 67.33% TST = 63.36%	Male gender (AOR 10.114, 95% CI 2.744–37.270; P = 0.001) and having pets at home (AOR 5.582, 95% CI 1.484–20.995; P = 0.015) are risk factors associated with the incidence of LTBI.	7

Cubilla-Batista (2019)[22]	-	Household contacts living with TB patients for at least 6 hours a day.	61	IGRA	11.5%	Being over 50 years old (OR= 29.5, 95% CI = 2.24–1,163) and overweight OR = 14.93, 95% CI = 1.57–483.3) are risk factors for the occurrence of LTBI.	4
Wardani (2021)[23]	Cross-sectional	Healthcare workers in TB service units and non-TB service units who do not have a history of TB illness or treatment.	128	TST	61.7%	Healthcare workers with a history of contact with TB patients at work (OR= 1.643, CI 95% 0.742-3.641) and who work for ≥8 hours a day are at risk of developing LTBI (OR=2.984, CI 95% 1.067-8.342).	7

Discussion

LTBI refers to a condition where an individual has been infected with TB but does not progress to active TB, thus not showing TB symptoms.[24] There are vulnerable groups at risk of developing LTBI that require to get TPT. These groups include individuals with HIV, adults and children who are household contacts of TB patients, undergoing dialysis patients, receiving anti-Tumor Necrosis Factor (TNF)-alpha medication patients, patients with silicosis, healthcare workers (including students in the health sector), immigrants from countries with a high TB burden, prisoners, homeless, cancer patients, those with diabetes mellitus, alcohol users, tobacco smokers, and individuals who are underweight.[6] Household contacts are defined as individuals who stay overnight or longer with TB patients, as well as those who frequently interact with TB patients within three months (even outside the home) before the TB patient is diagnosed.[25]

The journals or articles collected in this study indicate that certain individual characteristics are associated with a higher risk of developing LTBI. Research by Djibougou[21] found that men are at a 10.114 times higher risk of being infected with LTBI compared to women (AOR 10.114; 95% CI 2.744–37.270; P = 0.001). This finding is also supported by the study conducted by Nababan.[20] The high-risk is attributed to the fact that men often engage in outdoor activities that carry higher risks, such as herding, slaughtering, mining, and farming.[21] Other studies show that urban men are at a greater risk of developing LTBI due to the presence of social gathering places, such as bars, which are frequented more by men than women.[26] In contrast, research by Sangma[15] explains that women who are TB patients tend to pose a greater risk of exposing their household members to LTBI. This is due to the fact that many women are homemakers, spending more time at home, which increases the exposure duration for family members and raises their risk of contracting LTBI.[15]

Age is one of the risk factors for the occurrence of LTBI among household contacts of TB patients. Krishnamoorthy[17] noted that individuals over 18 years old contribute to an increased risk of developing LTBI. Another article by Odera[16] indicates that those aged 30-39 years and 40-49 years have a higher risk of developing LTBI compared to individuals aged 18-29 years. Research by Klayut[18] focusing on healthcare workers also found that individuals over 40 years old have a positive association with LTBI. Meanwhile, a study by Cubilla-Batista[22] stated that being over 50 years old is a risk factor for developing LTBI. Based on these four literatures, it is clear that over 18 years old has risk for the occurrence of LTBI. Nababan[20] explains that increasing age raises the risk of developing LTBI. This may be due to more frequent and prolonged exposure in the past, which increases the likelihood of prolonged exposure to and infection with TB, especially for those living in TB-endemic areas.[20] Additionally, the study mentions that the role of caring for TB patients is often taken on by older individuals, particularly within households. This results in older

individuals having longer and more intensive contact compared to younger family members who work outside the home.[20]

Other studies show that family members with certain types of occupations have a high-risk of developing LTBI. Karbito[19] stated that occupations such as farmers/laborers/fishermen are a dominant risk factor for the occurrence of LTBI (p=0.007; AOR=7.04; 95% CI=1.70–29.02). The article explains that jobs primarily involving outdoor activities carry a high-risk of LTBI infection. This study also suggests that TB transmission occurs not only within households but also in external environments, such as workplaces, schools, public transportation, and other communal places.[19]

Duration of employment is also a risk factor for LTBI. Research by Klayut[18] demonstrated that healthcare workers with more than 10 years of experience statistically have a significant association with the incidence of LTBI (AOR = 2.34, 95% CI: 1.05-5.21, p-value < 0.05). The study showed similar results by Meregildo-Rodrigues[27] indicating that healthcare workers frequently exposed to TB have a 2.28 times higher risk of developing LTBI. This is related to the frequent exposure experienced by healthcare workers and their interactions with TB patients in hospital. The more frequent and prolonged the exposure, the higher the risk healthcare workers face of developing LTBI.[19]

Duration of working hours also is a significant contributor to the risk of LTBI. Study by Wardani[23] clarified that healthcare workers who work ≥8 hours have 2.98 times risk for contributing to be LTBI. This is related to the duration of exposure in TB service units with high concentration of TB bacteria-containing droplets in the air inhaled by healthcare workers, which occurs more effectively. Without proper ventilation, TB infection can still occur in enclosed spaces.[1]

Have a history of contact with TB patients is one of the risks for developing LTBI. Wardani[23] explains that healthcare workers have 1.64 times the risk of developing LTBI if contact with TB patient. The findings of this study are consistent with the research by Karbito[19], which demonstrated that contact durations of ≥5 hours/day with TB patients can increase the risk of developing LTBI by 4.50 times (AOR: 4.70; 95% CI: 1.33–16.66). This may occur due to the high concentration of *Mycobacterium tuberculosis* released in airborne droplets, thereby increasing the likelihood of TB transmission, particularly among individuals sharing the same room with a TB patient.[1]

The findings from Krishnamoorthy[17] indicated a significant result concerning sharing a bedroom with TB patients, which has a 1.2 times higher risk of developing LTBI (Adj. IRR 1.2; 95% CI: 1.1–1.3, p-value: 0.04). The study explains that TB is transmitted not only through droplets from coughing or sneezing but can also be transmitted via small aerosols (1–5μm) that form when fluid in the bronchioles ruptures and remain airborne until inhaled by others. This

mechanism occurs not only during coughing but also during respiratory activities that generate aerosols, such as normal breathing—whether light or deep—like during sleep with snoring, which can trigger the release of aerosols potentially capable of transmitting TB.[17]

Bedroom density affects the incidence of LTBI. Karbito[19] explains that bedroom density is a risk factor for the occurrence of LTBI. An inadequate bedroom density (<8 m²/2 people) can increase the risk of LTBI by 5.33 times (95% CI: 2.24–12.71). This occurs because close proximity to TB patients increases exposure to aerosols containing TB bacteria. These findings indicate that the environment where exposure occurs plays a crucial role in the risk of LTBI. Household contact with the index patient presents a higher likelihood of proximity and greater exposure opportunities compared to other locations, even if household members do not share the same bedroom.[5]

Overweight is another risk factor for developing LTBI. Cubilla-Batista[22] demonstrated that obesity significantly increases the risk of LTBI among household contacts of TB patients (OR = 14.93, 95% CI = 1.57–483.3). Another study also showed similar results, indicating that being overweight can elevate the risk of LTBI.[19] Both studies did not explain why this occurs. However, research by Badawi[28] in the general population showed that Body Mass Index (BMI) has a negative correlation with the prevalence of LTBI ($r = -0.134$, $P < 0.01$). This means that higher BMI is associated with a lower likelihood of developing LTBI. Although no theory has yet explained this, the study suggests that nutritional factors and adiposity (fat accumulation in the body) can influence the immune system's ability to combat TB infections. There is a role of innate immunity mediated by cytokines such as Interferon-γ (IFN-γ), Tumor Necrosis Factor-α (TNF-α), and Interleukins (ILs), which play a crucial role in controlling TB infections.[28]

Another risk factor for the occurrence of LTBI is the presence of pets in the home. The study by Djibougou[21] indicates that having pets in the house is associated with a 5.582-fold higher risk of developing LTBI (AOR 5.582; 95% CI: 1.484–20.995; P = 0.015). This study explains that this may occur because animals can serve as reservoirs for *Mycobacteria*, including being a source of TB infection in humans. However, the research sampled not only household contacts of TB patients but also healthcare workers and employees in slaughterhouses, thus requiring further investigation specifically on the household contacts of TB patients.

This study certainly has limitations, including the study design which is a systematic review that examines several research studies from various literature databases. A systematic review can only explain based on what has been found in the journals or articles mentioned above. Additionally, only three databases were used with specific inclusion and exclusion criteria, which narrowed the scope of relevant literature and could potentially lead to selection bias. The risk factors considered are also very general, not specific to certain factors, making the discussion very broad. Recommendations for future research include using meta-analysis on the risk factors for LTBI in household contacts of TB patients to provide more scientifically valid results.

Conclusion

This research facilitates risk factors for LTBI among household contacts of TB patients, including age >18 years, male, occupation type (laborers/farmers/fishermen), duration of employment for >10 years, duration of working hours for ≥8 hours/day, contact with TB patients, sharing a bedroom with TB patients, bedroom density, overweight, and having pets. The government, healthcare workers, and the community, especially household contacts of TB patients, need to understand the risk factors for LTBI to prevent more comprehensive transmission, thus supporting the TB elimination program for 2030. Controlling LTBI requires specific strategies, especially for high-risk groups, such as household contacts of TB patients. However, further examination with different study designs using meta-analysis is needed to produce stronger studies as reference material for stakeholders in the development and prevention of LTBI.

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Conflict of Interest

We have no conflict of interest for this research.

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