SYSTEMATIC REVIEW

A Systematic Review of Prevalence and Risk Factors of Latent Tuberculosis Infection Among Medical and Nursing Students

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ABSTRACT

Introduction: Clinical training may expose medical and nursing students to workplace hazards comparable to those encountered by healthcare workers (HCWs). This study was designed to investigate the prevalence of latent tuberculosis infection (LTBI) and associated risk factors among medical and nursing students. **Methods:** Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, a systematic review was conducted utilising four electronic databases to appraise and synthesise the literature on LTBI which used the tuberculin skin test (TST) and the blood interferon-gamma release assay (IGRA). **Results:** Original articles published in the English language between 2010 and 2020 were included, yielding 14 relevant articles. The average prevalence of LTBI in high-burden countries was 38.2% for TST and 20.6% for the IGRA test. According to TST and IGRA findings, the average prevalence of LTBI in nations with an intermediate burden was 16.7% and 4.7 %, respectively. The average prevalence was 2.8% and 1.1% from the TST and IGRA tests for low-burden countries, respectively. A greater risk of LTBI was shown to be related with an increase in age among postgraduate medical school students, a history of Bacillus Calmette-Guerin (BCG) vaccination, origin from high-risk tuberculosis (TB) countries, increased hours of hospital exposure, a history of contact with TB cases, a high body mass index, older age group students, and a lower TB knowledge score. **Conclusion:** The available evidence from this review emphasised the importance of developing and implementing efficient and cost-effective TB infection-control programmes, particularly in high-burden countries and amongst students at risk.
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INTRODUCTION

Tuberculosis (TB) is an infectious illness that continues to be a serious global public health concern around the world. Given the availability of a range of very effective anti-TB medicines, tuberculosis remains a significant public health problem (1). In 2019, about ten million individuals were infected with TB and a total of 1.4 million people were reported to have died from TB (2). TB-controlled programmes are believed to be hampered by a variety of causes, including poor diagnostic performance, TB associations with other diseases such as HIV/AIDS and the development of multidrug-resistant (MDR) strains (3, 4).

Tuberculosis normally advances through three stages: primary TB infection, latent TB infection (LTBI) and active TB illness (5). LTBI is defined as the presence of an immune response to Mycobacterium tuberculosis antigen stimulation in the absence of clinical symptoms or signs of active TB (6). Individuals who have been diagnosed with LTBI are presumed to possess viable tubercle bacilli in their bodies. Although these tubercle bacilli are dormant, they can reactivate and cause diseases. While individuals with LTBI are neither infectious or contagious, they are nonetheless at risk of developing TB illness.

Around a quarter of the earth's population is believed to have LTBI, with a lifetime risk of becoming active tuberculosis of approximately 10% (7). Therefore, it is crucial to determine risk factors for the development of LTBI and progression to active TB (8). Healthcare workers (HCWs) are more likely to contract TB as a result of exposure to infected patients and insufficient infection control measures. The screening for LTBI in HCWs including medical students is strongly advised in order to get an early case diagnosis and prevent active TB disease progression. Appropriate screening for LTBI has become increasingly crucial and is regularly undertaken in low burden tuberculosis-endemic

countries as a result of the high number of immigrants coming from high burden tuberculosis-endemic regions (9, 10). Previous studies on the prevalence rate of LTBI mainly relied on the Mendel and Mantoux's tuberculin skin test (TST) (7). However, in the past few years, an increasing number of studies used the interferon-γ release assays (IGRAs) to diagnose LTBI, especially in high-income countries. IGRAs are more specific, have a larger negative predictive value and are not affected by BCG vaccination (11, 12).

The majority of published systematic reviews and meta-analyses available to date have concentrated on the prevalence of LTBI among HCWs in low-and/or high-burden TB countries, or limited to a certain screening method (13-15). HCWs are workers who had direct or indirect contact with patients and those who have been exposed to infected materials or the environment. These include doctors, nurses, therapists, laboratory assistants, administrative and cleaning staff. Because of the growing clinical exposure that medical and nursing students receive during their hospital rotations and clinical training, it is critical to assess the prevalence of LTBI among them (10). Furthermore, no comprehensive review on this topic has been published. Therefore, this systematic review was conducted to synthesise previously published data on the prevalence of LTBI among medical and nursing students using TST and/or IGRA testing, as well as determine its associated risk factors.

METHODS

Study protocol

A comprehensive evaluation of the available literature was conducted to ascertain the prevalence of LTBI among medical and nursing students. The results of this systematic review were presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (16).

Search strategy

To identify the latent tuberculosis studies among medical and nursing students, four bibliographic databases were searched: EBSCOHost MEDLINE Complete, Scopus, Science Direct and Proquest Central. An example of the strategy used to search in EBSCOHost MEDLINE Complete to identify studies for this systematic review showed in Table I. Initially, five broad concepts of 'prevalence', 'latent tuberculosis', 'TST', 'blood IGRA tests and 'medical or nursing students' were used as the keywords to identify subject searched in the databases. The 'OR' search operator was used to look for each search term in each database using the keywords and subjects above. To achieve the final search results, the search term for each concept were joined with 'AND'. Additionally, studies were hand-searched using reference snowballing techniques to identify additional publications that were missed by the database search.

Table I: Strategy used to search in EBSCOHost MEDLINE Complete database

Search ID#	Search Terms
Search #1	AB "prevalence" Limiters Date of Publication: 20100101-20201231 Human
Search #2	AB "Latent tuberculosis" OR "Tuberculosis" OR "latent OR latent tuberculosis" OR "latent tuberculosis infection" OR "mycobacterium tuberculosis"
Search #3:	TX "tuberculin test" OR "tuberculin tests" OR "tuberculin skin test" OR "tuberculin skin tests" OR "tst*" OR "mantoux*"
Search #4	TX "interferon-gamma" OR "interferon-gamma release assay" OR "interferon-gamma release assays" OR "interferon-gamma release test" OR "interferon-gamma release tests" OR "igra*"
Search #5	TX "medical student*" OR "medical resident*" OR "medicine student*" OR "students in medicine" OR "nursing student*" OR "student nurses"
Search #6	#3 OR #4
Search #7	#1 AND #2 AND #5 AND #6

Study selection: eligibility requirements

The systematic review used the following inclusion criteria: studies done in any country between 2010 and 2020, reporting on the prevalence of LTBI among nursing and medical students using TST and/ or IGRA, and written in English.

The following research were omitted from the review: those conducted on high-risk populations or on groups other than medical and nursing students. Additionally, intervention and cohort studies on selected positive tuberculosis cases, the population with specified TST or IGRA results as a necessary condition, and cost-effectiveness analyses were also excluded from the review. Moreover, any review articles and letters to the editor were not included in the review because they did not contain any primary data. Abstracts and non-English language studies were also omitted from the review (two non-English studies provided the abstract in the English language). If data duplication is detected, articles that present more detailed information on the outcomes of interest will be selected for review.

Study screening

To eliminate duplications, all identified records from multiple databases were entered into the ENDNoteX9 software, as well as additional records from relevant journals discovered through the grey literature search and hand-search. After removing the duplicates, three reviewers screened the records (ZI, MI and LHM) in two levels to evaluated for eligibility and final selection. The title and abstract were screened at the first level, while the full text was screened at the second level. During each stage of evaluation, reviewers assessed the records individually and then pooled their agreements. Before finalising the records for the next screening step, disagreements were addressed through discussion. Disagreements amongst the three reviewers were

discussed and resolved by consensus.

Quality assessment of the study

The quality of selected research was determined using the criteria for evaluating the quality of included studies on the prevalence of LTBI (7). Each research was evaluated based on four criteria: a) the quality of the sampling technique, b) the quality of the selection method, c) the quality of the response rate, and d) the assessment quality. On a three-point numeric value (0,1, or 2), these four criteria were measured. They included internal and external validity, as well as attrition bias, among other things. None of the studies was excluded from the review due to its low quality.

Data extraction

A Microsoft Office Excel document was used to extract the data. Data extracted includes:

a) Study characteristics: the author, the year of publication, the study location, the study design, the study year, the study settings, the participants, the total number of study participants, and the participants' age.

b) LTBI data: type of testing received, TST in-duration diameter cut-off used in each study, number of participants who had positive results for TST and/or IGRA. The data were extracted and presented separately for TST and IGRA, in the light of previously published evidence that the results of these two tests might be discordant (17). The LTBI was defined as a positive TST or positive IGRA as defined by the original authors.

c) Risk factors for positive LTBI among study participants as reported by the included studies

Data synthesis

A quantitative meta-analysis to explore possible relationships between the LTBI prevalence could not be used, given that several studies had different study participants, settings and country of origin from different TB risk burdens. Studies were also heterogeneous in many aspects, including cut-point tests that was used to detect LTBI, students' level by year of study and undergraduate and postgraduate classifications. Therefore, when available, the data was extracted for all participants in both the medical and nursing students population. A pooled estimate of LTBI prevalence was reported for LTBI diagnoses using either TST or IGRA that were categorised as high-burden, intermediate-burden and low-burden countries according to the World Health Organisation's (WHO) TB incidence interval countries' diseases burden (18). Significant risk factors for positive LTBI after the inferential analysis in individual studies were also included.

RESULTS

Search results

Three hundred and sixty-one records were found from databases and grey literature. Sixty duplicate records were removed and three reviewers screened the remaining 301 records. From these, 25 records were included in the full-text screening. Eventually, fourteen quantitative studies fulfilled the inclusion criteria for quantitative synthesis (Figure 1).

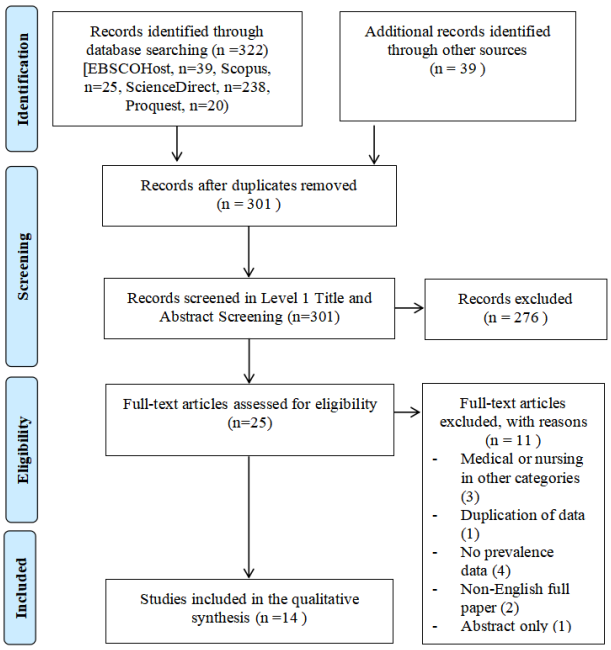

Figure 1: Flow diagram for selection of studies on latent tuberculosis infection among medical and nursing students

Study Characteristics

Table II shows fourteen studies with a total of 8,604 individuals from eight countries that were published between 2010 and 2020. Six from Italy (10,19-23), two from India (24-25), and one, respectively, from Iran (26), Malaysia (27), South Korea (28), Uganda (29), Saudi Arabia (30) and South Africa (31). These studies were conducted from 2007 through 2019 and published from 2010 through 2020. The study period was not reported in one study (27). All the studies used cross-sectional study designs. The sample size ranged from 79 to 2,466 subjects. Seven studies (19,20,22,26-28,31) were conducted amongst the medical students (31.8%), three studies (23,24,30) amongst the nursing students (13.6%) and four studies (10,21, 24,28) reported on both the medical and nursing students (18.2%).

Risk of bias

As indicated in Table III, the risk of bias and quality of the included studies were rated as being between 2 and 7 points. Only three of the studies employed the multiside sampling (19-21). All the studies provided the means of identification for TB. The response rate was not reported in two studies (20,25), whereby one study had a response rate of less than 65.0% (31). Six of the 12 studies presented findings for TST cut-off at 5 mm or 15 m (22,24,26,28,29,31). Indeterminate IGRA results constituted <10% were reported in two of the ten studies on IGRA (27, 31).

Table III: Scoring matrix for four quality assessment elements of all included studies (7)

Authors, year	Quality of sampling method [a]	Quality of selection method [b]	Response rate [c]	Quality of prevalence assessment		Total
				TST [d]	IGRA [e]	
Alian et al., 2016 (26)	0	2	2	2	-	6
Abdullah et al., 2019 (27)	0	2	2	-	2	6
Bonini et al., 2017 (19)	2	2	2	1	0	7/6
Christopher et al., 2010 (24)	0	2	2	2	-	6
Coppeta et al., 2019 (20)	2	2	0	-	0	4
Durando et al., 2013 (21)	2	2	2	1	0	7
Jung et al., 2012 (28)	0	2	0	2	0	4/2
Kinikar et al., 2019 (25)	0	2	0	1	0	3/2
Lamberti et al., 2014 (22)	0	2	2	2	0	6
Lamberti et al., 2015 (23)	0	2	2	1	0	5/4
Lou et al., 2015 (29)	0	2	2	2	-	6
Murad and Abdulmageed, 2012 (30)	0	2	2	1	-	5
van Rie et al., 2013 (31)	0	2	1	2	2	5
Verso et al., 2020 (10)	0	2	2	1	0	5/4

[a] '0' Convenience, '1' Randomization , '2'Multi-site randomization /National survey
[b] '0' No exclusion criterion stated / risk factor is an exclusion criterion, '1' Exclusion criterion stated (risk factor is not a criterion), '2'Means of identification of TB is stated
[c] '0'.Not recorded /reported, '1' Reported and < 65%, '2' Reported and 65% or above
[d] '0'TST cut-off at 10 mm was not present, '1' TST cut-off at 10 mm was present, '2'TST cut-off at 5 or 15 mm was present as well
[e] '0'Indeterminate IGRA results were not stated., '1' Indeterminate IGRA results were stated, '2' Indeterminate IGRA results constituted <10%

Prevalence of LTBI in the medical and nursing students

The individual data on TST and IGRA positivity for each study is shown in Table IV. Six studies reported the prevalence of LTBI using TST, three studies using IGRA and six studies using both TST and IGRA. Five of the published studies reported the prevalence of LTBI amongst medical and nursing students in high-burden countries, i.e., two from India (24,25) and one each from Uganda (29), Saudi Arabia (30) and South Africa (31). The reported prevalence ranged from 17.6% to 50.2% for TST and 16.2% to 22.5% for IGRA. The pooled prevalence was 38.2% (95% CI: 35.3-41.1%) and 20.6% (95% CI: 15.8-25.3%) according to TST and IGRA results, respectively.

Three studies reported the prevalence of LTBI from the intermediate-burden countries, which were from Iran (26), Malaysia (27) and South Korea (28). The pooled prevalence was 16.7% (95% CI: 13.2-20.1%) and 4.7% (95% CI: 2.3-7.2%) according to TST and IGRA results, respectively. Whereas, for the studies conducted in the low-burden countries, all six studies were conducted in Italy (10,19-23). The reported prevalence ranged from 1.0% to 6.3% for TST and 0.1% to 21.5% for IGRA. The pooled prevalence was 2.8% (95% CI: 2.4-3.2%) and 1.1% (95% CI: 0.9-1.4%) according to TST and IGRA results, respectively.

LTBI risk factors in medical and nursing students

Nine studies investigated the risk factors associated with LTBI in medical and nursing students. Three of the seven studies indicated that the older age group students were associated with positive LTBI diagnosis (10,22,25). The association between gender and LTBI was insignificant amongst the eight studies (20-22, 24-28). One study reported that positive LTBI was more frequently composed of a higher studying age and amongst postgraduate rather than undergraduate students attending medical schools (22). A history of BCG vaccination was significant in two out of the seven studies that reported on this risk factor (19,24). Study by Bonini et al. show previous BCG vaccination is a positive predictive value for positive TST outcome (19). Meanwhile, study by Verso et al. found a significance presence of students without BCG vaccination in students with LTBI (20).

All three studies that included the risk factor of 'individual origin from the high-risk countries' reported higher positivity of LTBI associated with this group (19,21,22). Additionally, the study by Durando et al. (21) also reported that TST positivity was associated with migrants

Table II: Characteristics of studies included in the systematic review

Authors, year	Country	Year of study	Study participants and setting	No. of participants	Age, Mean (SD)
Alian et al., 2016 (26)	Iran	2015	Medical students at Mazandaran University	297	22.4
Abdullah et al., 2019 (27)	Malaysia	NR	Year 1 and 5 medical students at the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia.	143 (68 Year 1, 75 Year 5)	Year 1 20±1 Year 5 23±1
Bonini et al., 2017 (19)	Italy	2014-2016	Medical students at, University of Parma	278	NR
Christopher et al., 2010 (24)	India	2007	Nursing trainees at Christian Medical College	436 (359 Undergraduate, 77 Postgraduate)	NR
Coppeta et al., 2019 (20)	Italy	2015	Medical Students at Teaching hospital in Rome	79	NR
Durando et al., 2013 (21)	Italy	2012	Medical and nursing students at San Martino-IST teaching Hospital of Genoa	733	23
Jung et al., 2012 (28)	South Korea	2010-2012	Medical students in second or third medical school in Seoul	153	21.9±0.9
Kinikar et al., 2019 (25)	India	2016-2017	Post graduate medical residents and nursing students Byramjee-Jeejeebhoy Government Medical College and Sassoon General Hospital in Pune, Maharashtra	200 (110 medical, 90 nursing)	Median age 25 (IQR, 19–27)
Lamberti et al., 2014 (22)	Italy	2012-2013	Undergraduate and postgraduate medical students attending Medical School, Second University of Naples	1726	25.76 ±5.3
Lamberti et al., 2015 (23)	Italy	2012-2013	Nursing students at Second University of Naples	1564	23.6 ± 5.4
Lou et al., 2015 (29)	Uganda	2009	Medical and nursing students students, Makerere University	262	Preclinical :22.4±2.6, Clinical: 25 ±2.8
Murad and Abdulmageed, 2012 (30)	Saudi Arabia	2010	Nursing students Health Sciences College for Girls, King Abdulaziz University Jeddah	108	NR
van Rie et al., 2013 (31)	South Africa	2008	Medical students in-patients and HIV clinic attendees at three public sector facilities in Johannesburg	77	Median 22 (IQR 22-24)
Verso et al., 2020 (10)	Italy	2014-2019	Undergraduate and postgraduate medical and nursing students School of Medicine, University of Palermo	2466 (1138 nursing, 464 undergraduate medicine, 864 post graduate medicine)	Undergraduate 23.80± 5.01, postgraduate 30.12 ± 3.15

NR: Not reported

students. Out of the three studies that included the hours of exposure to hospital environment, two studies reported a significant difference with increased positivity amongst those who spent more time at the healthcare centres or hospital environment (24,26). Furthermore, out of the six studies, two studies reported that students who had a history of contact with TB positive cases (26) or having prior exposure to sputum smear positive TB cases (25) were at a greater risk of prevalent LTBI. Other risk factors for LTBI included the high body mass index of above 25kg/m2 (25), higher studying age group (22) and lower TB knowledge score (31).

DISCUSSION

A total of 361 research papers, abstracts and theses were discovered after exploring on the multiple bibliographic databases and grey literature. Fourteen studies with 8,604 subjects for the medical and nursing students from eight countries; Italy, India, Iran, South Africa, Uganda, Saudi Arabia, South Korea and Malaysia were included for qualitative and quantitative analysis. However, the background of the TB prevalence for the eight countries varies significantly. For example, India, Uganda, Saudi Arabia and South Africa were considered TB high-burden countries. A country like Italy, the least impacted by tuberculosis, was classified as a low TB burden country in 2017, with a notification rate of 6.5 per 100,000 people. In contrast, Malaysia, Iran and South Korea were intermediate TB burden countries (32).

The result showed that the pooled prevalence of LTBI according to TST and IGRA tests amongst the medical and nursing students in high-burden countries were 38.2% and 20.6%, respectively. The pooled prevalence in intermediate-burden countries was 16.7% and 4.7% from TST and IGRA results, respectively. Whereas, for the studies conducted in a low-burden country, the pooled

Table IV: Diagnostic data and LTBI prevalence

TB incidence intervals (18)	Authors, year	Sample size	TST		IGRA		TST and IGRA			
			Platform; Cut Off; Reading Interval	TST + (% [95% CI]	Platform; Cut Off	IGRA + (%[95%CI])	TST Platform; Cut Off; Reading Interval	IGRA Platform; Cut Off	TST + (% [95% CI]	TST + & IGRA + (%[95%CI])
High burden countries	Christopher et al., 2010	436 nursing student	2 TU RT 23;≥10mm; 48–72h	219/436 (50.2 [45.5-54.9])						
	Murad and Abdulmageed, 2012	108 nursing students	5 TU Tubersol; ≥10 mm; NR	19/108 (17.6 [10.4-24.8] 24.8)						
	Lou et al., 2015	262 medical and nursing students	2 TU RT 23; ≥10 mm; 72 h	113/262 (43.1 [37.1-49.1]						
	van Rie et al., 2013	77 medical students					2 TU RT 23; ≥10mm;48–72 h	QFT-TB Gold; > 0.35 IU/mL	21/77 (27.3 [17.3-37.2])	12/74 (16.2 [8.7-26.6])
	Kinikar et al., 2019	200 medical and nursing students					5 TU Tubersol; ≥10 mm; 48–72 h	QFT-TB Gold ; > 0.35 IU/mL	42/200 (21.0 [15.4-26.6])	27/200 (22.5 [16.5, 30.0])
Intermediate burden countries	Alian et al., 2016	297 medical student	5 TU Tubersol; ≥10mm;48–72h, <10mm repeated after 1-3 weeks	52/297 (17.5 [13.2-21.8])						
	Abdullah et al., 2019	143 medical student			QFT-Plus ELISA; > 0.35 IU/mL	6/143 (4.2 [0.9-7.5]				
	Jung et al., 2012	153 medical student					2 TU RT 23; ≥10 mm; 48–72h	QFT-TB Gold; > 0.35 IU/mL	23/153 (15.0 [9.4-20.7])	8/23 (34.8 [16.4-57.3])
Low burden countries	Bonini et al., 2017	278 medical student	5 TU Tubersol; ≥10mm;48–72 h	8/278 (2.9 [0.9-4.8])						
	Coppeta et al., 2019	79 medical student			QFT-TB Gold ; > 0.35 IU/mL	17/79 (21.5 [12.5-30.6])				
	Durando et al., 2013	733 medical and nursing students					2 TU RT 23; ≥10 mm;48–72h	QFT-TB Gold ; > 0.35 IU/mL	10/733 (1.4 [0.55-2.2])	4/10 (40.0 [12.2-73.8])
	Lamberti et al., 2014	1727 medical students					2 TU RT 23; ≥10 mm;72-96 h	QFT-TB Gold ; > 0.35 IU/mL	109/1726 (6.3 [5.2-7.5])	23/110 (20.9 [13.7- 29.7])
	Lamberti et al., 2015	1564 nursing students					2 TU RT 23; ≥10 mm; 72-96 h	QFT-TB Gold ; > 0.35 IU/mL	19/1562 (1.0 [0.5-1.4])	2/21 9.5 (1.2-30.4)
	Verso et al., 2019	2466 medical and nursing students					5 TU Tubersol; ≥10 mm healthy,≥5 mm contact;48–72h	QFT-TB Gold; > 0.35 IU/mL	44/2466 (1.8 [1.3-2.3])	29/44 65.9 (50.1-1.6)

prevalence was 2.8% and 1.1% according to TST and IGRA results, respectively. Although the prevalence was stratified based on the test used, the pooled averages should be regarded with care due to the heterogeneity of the results. The pooled prevalence in this study review was almost comparable to the previously reported pooled prevalence, which was 26% based on the TST test in high-burden countries between 2001 to 2015 (33). According to another systematic review, the global prevalence of LTBI was 24.8% based on IGRA and 21.2% based on TST, respectively (7). Meanwhile, in high-burden nations, the total prevalence of all types of HCWs was 55% positive for TST and 56% positive for IGRA. (13). Despite the fact that medical and nursing students have a lower prevalence of LTBI than HCWs, they require similar attention as needed by HCWs

since their risks of LTBI are still greater than the general population (13,34).

Generally, most of the studies that assessed the LTBI prevalence by TST showed a higher prevalence compared to IGRA only, or both TST and IGRA methods. This was due to the fact that positive TST could also be found in those with previous BCG vaccination and those infected by non-tuberculous mycobacteria (35). IGRA is more specific and sensitive (36) as it targets the RD-1 specific antigen. Nevertheless, a comparison study between TST and IGRA showed that neither TST nor IGRA could predict the subsequent development of active TB amongst household contact of pulmonary TB patients (17). Furthermore, future research and review on the concordance rate between the two tests of TST and IGRA for LTBI diagnosis is suggested, as our study found that while IGRAs may have a relative advantage over TST in detecting LTBI, TST remains the most preferred method for LTBI diagnosis in resource-limited, high-TB-burden settings (24,25,29).

A study conducted among young nursing trainees in South India using the TST test found that the highest prevalence of LTBI was 50.2% (24). One of the reported reason for the high-prevalence was due to the increased and repeated exposures of the TB patients in healthcare facilities. Tuberculosis is a significant public health problem in India, which has the highest rate of infection, with an estimated incidence of 2.64 million cases in 2019 (37). Other factors that might influence the higher rate of LTBI prevalence in India include poor adherence to treatment, delay in diagnosis, delay in initiation of anti-TB drugs amongst smear-positive patients, overcrowded wards and lack of infection control measures (38,39). A study amongst medical and nursing students in India reported a prevalence of 21% and 22.5% by the TST and IGRA tests, respectively, whereby prior exposure to sputum smear-positive TB cases was linked to an increased likelihood of prevalent LTBI (25).

Additionally, a study in Uganda found that 45.1% of medical and nursing students had LTBI (29). These two studies from India and Uganda might have influenced the overall prevalence rate of LTBI tested using the TST approach in high-burden countries since both prevalence rates were significantly higher. The increase in exposure related to clinical work suggested tuberculosis nosocomial exposure amongst the medical and nursing students in Uganda. There were six studies conducted in Italy amongst medical and nursing students, whereby four studies detected LTBI using TST and IGRA tests, and the prevalence ranged from 0.1% to 1.2%. The prevalence of LTBI in Italy is relatively low. Amongst the TST, positivity cases were reported associated with immigrants.

The availability of an effective treatment for LTBI will substantially reduce the progression of LTBI to active disease. Furthermore, preventive therapy for LTBI has been available for more than 60 years to prevent the progression of active TB disease. The WHO's End TB Strategy has emphasised the importance of patient-centred care and expanding access to LTBI prevention treatment to reduce the reservoir of latently infected people. There are currently four treatment regimens available for LTBI (40). The regimen consisted of isoniazid for six to nine months, rifampicin daily for four months, isoniazid and rifapentine weekly for three months, and isoniazid and rifampicin daily for three to four months (41). More people in low and middle-income countries would be able to get treatment if they were given a shorter treatment regimen that was easier to finish and less toxic, thereby closing the gap in the last phase of the LTBI cascade (42).

There were nine studies analysing the individual risk factors alongside the LTBI prevalence. Two studies reported BCG vaccination as a significant risk factor (10,19). Previous meta-analysis studies have reported that patients who had received BCG vaccination were more likely to have a positive tuberculin skin test as also reported by Bonini et al (19,43). While other studies also showed the BCG vaccine has a significant protective effect against LTBI, as reported by Verso et al. (10, 44, 45). While four studies show no significant relationship between the history of BCG vaccination and positive LTBI. The BCG vaccine against TB is widely used in TB endemic countries, including India, Uganda, South Africa, Iran, Saudi Arabia, Malaysia, and South Korea. BCG vaccination has reached a worldwide coverage of more than 80% in low-and middle-income countries in 2019 (46). However, in Europe, the guidelines for its use vary greatly from country to country. Italy, for example, has mandatorily discontinued BCG vaccination requirements for all students enrolled in medical faculties since 2001 (10). Furthermore, the BCG vaccination is not included in Italy's national immunisation schedules. The effectiveness of the BCG vaccine against pulmonary TB is highly variable, ranging from 0 to 80% and will decline with time (47). Thus, study on these variables among the medical and nursing students is essential towards eradication and prevention of the spread of TB as they are also exposed to the risk of getting the diseases particularly in high burden countries.

The findings in three studies reported the older age group students as a risk factor (10,22,25). and three studies reported the origin from high-risked countries associated with higher positivity of LTBI (19,21,22). Other risk factors include the increase in time spent at the hospital (24,26), history of contact with TB cases (25,26), high body mass index of above 25kg/m2, (25) and lower TB knowledge score (31). Moreover, most of the risk factors were similar to those reported in previous reviews and studies (13,15,48). The high cases of LTBI among the medical and nursing students suggested that a proper guideline should be made to decrease the risk

of TB infections. As a result, these risk factors, together with the high prevalence of LTBI among medical and nursing students, particularly in high-burden countries, may imply that further measures are needed to ensure that these students receive the necessary protection.

This study had a few limitations, whereby the review only included studies that documented the prevalence of LTBI published in the English language. Therefore, data from studies that were published in other languages might be excluded. Secondly, due to varying sampling techniques, thus the quality for the crude estimation of prevalence might differ across the study. Finally, the studies were heterogeneous due to differences in the study locations, tests, respondents, methodological quality, contacts with TB patients and control measures across the studies. As a result, the study was unable to conduct the meta-analysis.

CONCLUSION

Data on the prevalence of LTBI and related risk factors among medical and nursing students in countries with high, intermediate, and low TB burdens were presented in this systematic review. Numerous studies have been undertaken on this subject but the numbers of studies remains limited. The findings from this study also demonstrated that medical and nursing students, particularly in high TB burden countries, continued to be at an elevated risk of TB infection despite the variability amongst the studies. Therefore, necessary actions, such as regular screening for LTBI amongst students undergoing clinical training should be in place, so that early treatment can be given in order to reduce the risk of active TB. Furthermore, in healthcare institutions, a comprehensive TB infection control strategy that includes administrative, environmental, and personal protective measures is required.

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